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UTAH SUPREME COURT

BRIEF

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IN THE SUPREME COURT OF THE STATE OF UTAH

ILO MARIE GRUNDBERG, Individually and JANICE GRAY, a personal representative of the Estate of Mildred Lucille Coats, deceased Respondents and Appellees, V. THE UPJOHN COMPANY, Petitioner and Appellant.	:	Case No. 900573 Category 12

PETITION FOR REHEARING OF APPELLEES, ILO MARIE GRUNDBERG Individually, and JANICE GRAY, as personal representative of the Estate of Mildred Lucille Coats

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APPENDIX TO PETITION FOR REHEARING ON CERTIFIED QUESTIONS TO THE SUPREME COURT OF UTAH BY THE UNITED STATES DISTRICT COURT, DISTRICT OF UTAH, CENTRAL DIVISION, HONORABLE J. THOMAS GREENE, JR.

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FILED

JUN 11 1991

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UTAH

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Union Calendar No. 294

98th Congress, 1st Session - - - - - - - - - - House Report No. 98-511

DEFICIENCIES IN FDA'S REGULATION OF THE NEW DRUG "ORAFLEX"

FOURTEENTH REPORT

BY THE

COMMITTEE ON GOVERNMENT OPERATIONS

together with

ADDITIONAL VIEWS

NOVEMBER 9, 1983.—Committed to the Committee of the Whole House on the State of the Union and ordered to be printed

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U.S. GOVERNMENT PRINTING OFFICE

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LETTER OF TRANSMITTAL

HOUSE OF REPRESENTATIVES,
Washington, D.C., November 9, 1983.

Hon. THOMAS P. O'NEILL, Jr.,
Speaker of the House of Representatives,
Washington, D.C.

DEAR MR. SPEAKER: By direction of the Committee on Gover ment Operations, I submit herewith the committee's fourteer report to the 98th Congress. The committee's report is based or study made by its Intergovernmental Relations and Human I sources Subcommittee.

JACK BROOKS, *Chairman*

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Union Calendar No. 294

98TH CONGRESS | HOUSE OF REPRESENTATIVES | REPORT
1st Session | | No. 98-51

DEFICIENCIES IN FDA'S REGULATION OF THE NEW DRUG "ORAFLEX"

NOVEMBER 9, 1983.—Committed to the Committee of the Whole House on the State of the Union and ordered to be printed

Mr. BROOKS, from the Committee on Government Operations, submitted the following

FOURTEENTH REPORT

together with

ADDITIONAL VIEWS

On October 25, 1983, the Committee on Government Operation approved and adopted a report entitled "Deficiencies in FDA's Re ulation of the New Drug 'Oraflex'." The chairman was directed t transmit a copy to the Speaker of the House.

I. INTRODUCTION

Under the rules of the House of Representatives, the Committe on Government Operations has responsibility for studying the ope ation of Government activities at all levels from the standpoint economy and efficiency. The committee has assigned this respons bility as it relates to the Department of Health and Human Ser ices (HHS) to the Intergovernmental Relations and Human R sources Subcommittee.

Since 1964 the subcommittee has periodically examined the pe formance of the Food and Drug Administration (FDA) in protectin the public from unsafe and ineffective drugs.

FDA's central responsibility, in the drug area, is to regulate th investigational use of new drugs and to evaluate applications fc marketing new drug products. In discharging this responsibilit FDA is expected to obtain and review all available information re evant to the safety and efficacy of new drug products before a proving them for marketing.

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Inasmuch as HHS had recently announced plans to speed the approval and marketing of new drugs, the subcommittee believed it was timely, as well as important, to assess the soundness of FDA's current policies and procedures for insuring the availability and thorough review of all important information concerning new drugs. As part of this assessment, the subcommittee's inquiry focused on FDA's review of Oraflex (generic name benoxaprofen), a newly approved anti-arthritis drug manufactured by Eli Lilly and Company (Lilly).

The subcommittee's ongoing investigation of FDA's review of Oraflex has included two days of public hearings on August 3 and 4, 1982.[1]

Witnesses included the Commissioner of the Food and Drug Administration, the Director of FDA's National Center for Drugs and Biologics, and the Acting Director of FDA's Office of New Drug Evaluation.

The subcommittee investigation of FDA's evaluation and approval of Oraflex included careful examination of the relevant medical literature and of FDA documents, including correspondence, internal memoranda, establishment inspection reports, and information contained in the Oraflex new drug application (NDA) and investigational new drug (IND) files. In addition, the subcommittee obtained information on Oraflex from both public and private sources outside the United States. The comprehensive nature of this documentation enabled the subcommittee to evaluate the adequacy of FDA's policies and procedures for insuring the safety and effectiveness of new drugs in general and Oraflex in particular.

II. Background

The FDA approved Oraflex on April 19, 1982, for relief from the pain and inflammation of rheumatoid and osteoarthritis. Oraflex was one of several nonsteroidal anti-inflammatory drugs (NSAID's) approved for this purpose by the FDA. Because of its exceptionally long half-life or retention period in the body, Oraflex offered the advantage (shared by only one other approved NSAID [2]) of once-a-day dosage.

Oraflex was first synthesized in 1966 by its manufacturer, Eli Lilly and Company, at its research center in the United Kingdom. In the United States, Lilly submitted an investigational new drug application (IND) for Oraflex on June 10, 1974, and a new drug application (NDA) on January 17, 1980. Approximately 3,000 users and 105 clinical investigators participated in the Oraflex clinical trials in the United States.

The question of whether Oraflex should be approved was referred by FDA to its Arthritis Advisory Committee. In a January 21, 1982, meeting, the committee unanimously voted to recommend approval of the drug. However, it expressed concern about the drug's side effects, especially phototoxicity. For Oraflex patients

[1] Hearings before a Subcommittee of the Committee on Government Operations, House of Representatives, "The Regulation of New Drugs by the Food and Drug Administration: The New Drug Review Process," August 3 and 4, 1982, hereinafter referred to as Hearings.

[2] On April 6, 1982, FDA had approved Feldene, which is manufactured by Pfizer Pharmaceuticals.

this involved burning, itching, redness and sometimes wheals after brief exposure to sun or ultraviolet light. Concern also was shown for Oraflex patients who developed onycholysis, the loosening or separation of the fingernail from its bed. The Advisory Committee decided that Oraflex-induced phototoxicity and onycholysis were generally minor problems that could be handled by appropriate warnings in the drug's labeling.

On April 19, 1982, approximately three months after the Arthritis Advisory Committee meeting, Oraflex was approved by FDA for marketing in the United States. By this time, the drug had already been marketed in the United Kingdom for approximately 18 months.[3]

Five days after FDA approved Oraflex, an article appeared in The Lancet, a British medical journal, linking Oraflex to three cases of jaundice in the United Kingdom.[4] On May 8, 1982, 19 days after FDA approved Oraflex, the British Medical Journal published an article on the benoxaprofen-associated deaths of five elderly women in Northern Ireland who developed jaundice and, in all but one case, kidney disease. The article also mentioned a sixth patient who died of kidney failure.[5]

On May 27, 1982, FDA received a letter dated May 20, 1982, from a senior government medical official in the United Kingdom who enclosed a February 1982 adverse reaction register associating the drug with 27 deaths in the United Kingdom, including 15 deaths from gastrointestinal disorders, two deaths from liver failure, and three deaths from kidney disease.[6]

In the wake of British reports linking Oraflex with fatal liver disease, the Arthritis Advisory Committee devoted its June 3-4, 1982, meeting to a consideration of the liver toxicity of the nonsteroidal anti-inflammatory drugs, including Oraflex. Following the meeting, FDA advised Lilly to modify the Oraflex labeling. On July 12, 1982, FDA approved revised labeling which acknowledged reports of Oraflex-associated deaths from liver and, in many cases, kidney disease. Noting reports of deaths among elderly users of the drug, the labeling also recommended one-half to two-thirds of the usual dose for older patients.

On July 22, 1982, Lilly advised FDA that the Danish drug regulatory authority had decided to restrict use of benoxaprofen to hospitals, beginning August 2, 1982.[7] The Danes based this action on reports in the British medical literature and the high incidence of drug-related skin reactions. The Danish regulatory authority had also received three reports of drug-associated deaths, two of which involved liver dysfunction.[8]

At the time of the subcommittee hearing on August 3, 1982, 1(benoxaprofen-associated deaths had been reported in the Britis

[3] It was approved in the United Kingdom for hospital use only in May 1980, and for general commercial marketing in October 1980.

[4] This April 24, 1982, article is reprinted at page 105 of the Hearings.

[5] Hearings, page 104.

[6] The letter and register are on file in the subcommittee office.

[7] See memorandum of July 28, 1982, meeting between FDA staff and Lilly representatives subcommittee files.

[8] Ibid

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medical literature,[9] including 14 from liver and/or kidney failure, one from gastro-intestinal disease, and one from a serious skin disorder. In addition, FDA had received from the British Government's Committee on Safety of Medicines a June 1982 adverse reaction printout showing 33 benoxaprofen-associated deaths in the United Kingdom, including 19 from gastro-intestinal disorders, 3 from liver diseases, 3 from kidney failure, and 3 from skin diseases.[10] Just minutes before the subcommittee hearing commenced on August 4, the Committee on Safety of Medicines notified FDA that it had suspended the product's license in the United Kingdom for 90 days.[11] By this time, British health officials had received more than 3,500 reports of benoxaprofen-associated adverse effects, including 61 reports of deaths.[12]

In announcing the British decision at the subcommittee hearing that morning, FDA Commissioner Arthur Hull Hayes, Jr., stated that FDA was "in the process now of finding out from [the British] what data they have, the basis for this, so that we can act appropriately." [13] Immediately following the subcommittee's hearings, FDA officials met with representatives from Lilly to discuss the British Government's action. Later that same day, Lilly announced that distribution of benoxaprofen would be suspended worldwide. The drug had been marketed in West Germany, South Africa, Denmark, Spain, Hong Kong, Malaysia, Singapore, and Thailand, as well as in the United States and the United Kingdom. At the time Lilly removed Oraflex from the market, it had been associated with 11 reported deaths in the United States. Oraflex has more recently been associated with 36 deaths from liver and/or kidney disease and 7 deaths from gastrointestinal disorders in the United States.[14]

III. Findings and Conclusions

A. FDA failed to review all significant Oraflex safety information in its possession prior to approving the drug

1. FDA did not insure that its reviewers examined all files containing reports of Oraflex-associated adverse effects

To meet the FDA requirement for reporting all significant adverse reactions associated with drugs under investigation, drug sponsors may elect to make such reports to the IND (investigational new drug) file rather than to the NDA (new drug application) file. In fact, FDA has not expected adverse reaction reports would be made to the NDA file after the sponsor of an NDA has declared a "data lock point"—the point at which the sponsor determines that it has reported to the NDA file all safety and efficacy data

[9] All of these deaths appeared in the British Medical Journal. One was reported in the January 16, 1982, issue; 6 in the May 8, 1982, issue; 3 in the May 29, 1982, issue; 3 in the June 12, 1982, issue; 2 in the July 3, 1982, issue; and 1 in the July 31, 1982, issue.

[10] This printout, which is in the subcommittee files, may have included some of the 16 drug-associated deaths reported in the British medical literature.

[11] Memorandum by Jerome Halperin, Acting Director, Office of Drugs, of an August 4, 1982, telephone conversation with Dr. Gerald Jones, Medicines Division, U.K. Department of Health and Social Security. On file in subcommittee office.

[12] Ibid.

[13] Hearings, page 368.

[14] October 7, 1983, tri-weekly FDA submission from Lilly of adverse experience reports, which is in subcommittee files.

needed to support the new drug application. Since, as FDA officials testified, the NDA is the primary file for drugs under NDA review, the committee believes it imperative that FDA require full and prompt reports to that file up to the date of NDA approval.

FDA acknowledged during subcommittee hearings that it has not routinely required its staff charged with evaluating new drug applications to examine the IND file for reports of adverse reactions before they approve new drugs for marketing. This policy resulted in the agency's failure, prior to approving Oraflex, to detect several important reports of Oraflex-associated liver and kidney reactions that had occurred during clinical trials. FDA approved labeling for Oraflex which made no mention of drug-associated liver reaction reports and even erroneously denied the existence of kidney disease in the clinical trials.

FDA's lack of awareness, when it approved Oraflex, of the clinical trial reports it had already received of liver and kidney disease proved particularly unfortunate in the light of the numerous reports received of fatal as well as nonfatal drug-associated liver and kidney injury after the drug's approval.

2. FDA approved Oraflex without knowing whether it had received all reports associating the drug with deaths and other serious adverse reactions

After receiving information that Lilly did not report to FDA several benoxaprofen-associated deaths known to its United Kingdom division prior to the approval of Oraflex in the United States, the subcommittee asked FDA whether the firm had reported any benoxaprofen-associated deaths occurring outside the United States before FDA approval. FDA initially responded that it did not know more than five months after approving Oraflex, whether Lilly had made such reports. It is evident from FDA's response that it had not thoroughly examined the sponsor's IND and NDA submissions before approving the drug for marketing.

Moreover, because of a filing backlog in the documents room of the division charged with reviewing the Oraflex NDA, FDA was unable to determine whether the sponsor had reported any significant adverse reactions in the several months immediately preceding the drug's approval on April 19, 1982. FDA was unable to review several reports of significant liver and kidney disease which had been reported during that period.

On June 23, 1982, more than two months after Oraflex was approved, Lilly informed FDA that five cases of jaundice had occurred during the clinical trials, three of which had not been reported. The drug's labeling did not mention jaundice and, in fact two company vice-presidents had stated earlier that no cases of jaundice had occurred in the clinical trials. On July 2, 1982, Lilly informed FDA that it had reported all of the clinical trial cases involving jaundice prior to the drug's approval, and that all of them had also involved serious kidney disease. Despite Lilly's discrepant versions of what it had reported, FDA, as late as the August hearing, had still not confirmed and, in fact, was unable to confirm, whether the firm had reported cases of Oraflex-associated liver and kidney reactions prior to the Oraflex approval.

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B. PRIOR TO APPROVING ORAFLEX, FDA MADE NO EFFORT TO OBTAIN INFORMATION ON ITS SAFETY FROM FOREIGN COUNTRIES IN WHICH IT WAS ALREADY MARKETED

Despite its responsibility to consider all available information relevant to a new drug's safety, FDA has instituted no procedures for seeking adverse reaction data for drugs under investigation in the United States which have already been marketed in other countries. As a result, FDA was not aware of several deaths and other serious adverse reactions associated with Oraflex which had been reported to British health authorities prior to the drug's approval on April 19, 1982. For example, a February 1982 adverse reaction register for Oraflex which FDA received from British medical officials more than a month after it approved the drug showed 27 deaths and 25 reports of nonfatal liver and nine reports of nonfatal kidney disease among the drug's users in the United Kingdom.

Report data from other countries also might have been available to FDA prior to its approval of Oraflex. The Danish regulatory authority, for example, received reports of 143 adverse reactions and three deaths associated with use of the drug in a 10-month period prior to this date.

The committee believes FDA should make full use of the marketing experience of other nations with drugs that are under NDA review, particularly since premarketing studies frequently do not include a sufficient number of patients to detect unanticipated and relatively infrequent adverse reactions. Foreign marketing data can provide FDA with an indispensable source of information on the types and frequency of serious side effects reported for drugs under investigation in the United States.

C. LILLY DID NOT REPORT SERIOUS ADVERSE REACTIONS ASSOCIATED WITH USE OF ORAFLEX PRIOR TO APPROVAL OF THE DRUG

FDA regulations require sponsors to supply the agency with prompt and full reports of "any finding" associated with a drug under investigation that may prove pertinent to its safety. The subcommittee's investigation has revealed that Eli Lilly and Company did not report to FDA at least 32 benoxaprofen-associated deaths outside the United States known to its foreign affiliates prior to FDA approval of the drug. In addition, several officials in Lilly's Indianapolis headquarters were advised of a number of unreported Oraflex-associated deaths outside the United States before the drug was approved.

Despite FDA's requirement that it receive prompt and full reports of "any finding" associated with an investigational new drug which may significantly relate to that drug's safety, FDA officials have expressed the belief that sponsors are not always reporting to FDA deaths and other significant adverse experiences associated with the foreign marketing of drugs under investigation in the United States and that Lilly's failure to make such reports appeared consistent with current industry practice. The committee believes that FDA cannot carry out its statutory responsibility for protecting the public from unsafe drugs unless it promptly receives

complete reports of all known deaths and serious adverse effects as sociated with new drugs, wherever they occur.

More than a year before the FDA initiated an inspection o Lilly's Oraflex records on October 18, 1982, an agency official ha recommended the prosecution of those Lilly officials responsible fo allegedly failing to report "important adverse findings" about Ora flex and several other drugs. FDA had been investigating Lilly's re porting practices since the fall of 1979. At the subcommittee' August 3, 1982, hearing, FDA officials characterized this investiga tion as "full-fledged" and "ongoing." Despite this, the agency di not undertake its inspection of Lilly's report files concerning Ora flex-associated deaths outside the United States until advised b the subcommittee of the company's failure to report 13 such death prior to the drug's approval on April 19, 1982. Based solely on th findings of this inspection, which uncovered additional unreporte Oraflex-associated deaths, FDA requested the Justice Departmer to initiate a grand jury investigation.

D. FDA ENFORCEMENT OF ITS ADVERSE REACTION REPORTING REQUIREMENTS WAS INADEQUATE

Shortly after FDA discovered unreported Oraflex deaths by i specting Lilly records in late 1982, the supervisory medical offic in FDA's Oraflex review found that Pfizer Pharmaceuticals al failed to report to FDA several serious adverse reactions, includi one death, associated with use of its arthritis drug, Feldene, outsi the United States prior to FDA approval of that drug. This bears strong resemblance to the Oraflex situation. Pfizer did not infor FDA of serious adverse reactions which apparently were report to its foreign divisions prior to FDA's approval of Feldene. How er, no referral of the Pfizer matter was made to any investigati arm of the FDA.

The committee questions FDA's commitment to enforcing its re ulations requiring sponsors promptly to report all significant safe information relating to drugs under investigation. In this conn tion, the committee notes that FDA did not investigate the exte of Lilly's failure to report Oraflex-associated deaths outside t United States until after it had been advised by the subcommitt of 13 such unreported deaths.

The FDA is charged with executing the Food, Drug, and Cosm ic Act and its implementing regulations. The committee belie FDA places the public's health at risk when it does not vigorou enforce the legal requirement that a sponsor report all adverse actions to a new drug under clinical investigation, since this inf mation is needed to weigh the risks of the drug against its pot tial benefits.

IV. RECOMMENDATIONS

The committee recommends that the Secretary of Health Human Services take prompt action to assure the correction of deficiencies identified in this report. The committee specifically ommends that:

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1. FDA require sponsors to report all adverse drug reactions simultaneously to both the investigational new drug (IND) and new drug application (NDA) files for drugs under investigation.

2. FDA evaluate all reports it receives of adverse reactions associated with new drugs before approving such drugs for marketing. Steps should be taken to:

a. Assure a thorough examination of all documents and files which might contain such reports;

b. Establish for drug sponsors standardized formats for recording and alerting FDA reviewers to serious adverse reactions; and

c. Assure that all incoming adverse reaction reports for drugs under investigation are promptly and systematically entered into appropriate files and are immediately retrievable for review.

3. FDA establish procedures for obtaining information concerning the safety and effectiveness of drugs under investigation from foreign countries in which such drugs have already been approved, or disapproved, for marketing.

4. Institute policies and procedures for insuring that the agency's adverse reaction reporting requirements are strictly enforced.

V. Deficiencies in the FDA Review of Oraflex

A. FDA failed to review all significant Oraflex safety information in its possession prior to approving the drug

During a 1981 inspection, FDA investigators learned that Lilly had reported significant adverse reactions to the Oraflex NDA which it had not reported to the Oraflex IND, and vice versa.[15] FDA, however, has not required firms to submit reports of serious or alarming adverse effects to both the active IND and NDA files for drugs under investigation. While acknowledging during the subcommittee's hearings that once a new drug application is filed, "the primary attention of the reviewers is on the NDA and not the IND," [16] FDA informed the subcommittee on October 22, 1982, that it "has not ordinarily expected most additional adverse reaction data to be submitted to the NDA" [17] following the establishment of a data lock point—the point at which the sponsor decides no longer to provide full reports and analysis of efficacy and safety information to the NDA file. Lilly set its data lock point for Oraflex in November 1978, almost 3½ years before FDA approved the drug. During this interval, FDA neither required nor expected Lilly to submit significant Oraflex-associated adverse effects to the Oraflex NDA.

FDA has acknowleged that it has established "no policy, written or unwritten, freeing sponsors from reporting any significant adverse reactions that our regulations otherwise require them to report." [18] FDA regulations, in fact, require full reports to FDA of

[15] Hearings, page 75.
[16] Hearings, page 120.
[17] Hearings, page 559.
[18] Hearings, page 559.

significant information pertinent to the safety of a new drug under investigation.[19] Since the NDA is the primary file for a drug under NDA review, the committee believes it imperative that FDA require full and prompt reports of significant adverse effects to that file up to the date of NDA approval.

Dr. Robert Temple, Acting Director, FDA's Office of New Drug Evaluation, acknowledged during the subcommittee hearings, that the agency did not routinely require the staff charged with reviewing new drug applications to examine, before approving a new drug, the IND file for legally required reports of drug-associated adverse effects which may not have been submitted to its companion NDA file.[20] Despite Dr. Temple's statement that "it would be very unusual • • • to find a major adverse reaction in [the IND file] once an NDA had been submitted," [21] the subcommittee investigation revealed that several important Oraflex-associated liver reactions which the sponsor had reported only to the IND had escaped the notice of agency reviewers prior to FDA's approval of the Oraflex NDA. Had such reports been noted, it is unlikely that FDA would have originally approved labeling for the drug which made no mention of liver disease and which confined Oraflex-associated liver reactions to "liver function test abnormalities" which were "usually transient." [22]

The subcommittee's investigation revealed that before FDA approved this labeling on April 19, 1982, Lilly had reported four cases of serious liver disease to the Oraflex IND, all of which involved clinical trial patients who had also developed kidney disease. The first such case was reported more than 15 months before Lilly submitted its new drug application for Oraflex on January 17, 1980. Lilly included in an October 5, 1978, IND submission, a drug experience report for a 60-year-old patient who developed jaundice. This patient also eventually developed kidney disease. In fact, she was admitted to the hospital on August 28, 1978, in hepato-renal failure and required renal dialysis.[23]

A 70-year-old female patient featured in a February 23, 1982, IND submission, showed a similar course. This patient developed hepatitis, jaundice, and, according to a preliminary report, acute renal failure secondary to nephritis while taking Oraflex.[24]

A March 22, 1982, IND submission described a case of drug-induced liver and kidney disease involving a 60-year-old female clinical trial patient on 1,000 mg/day of Oraflex who suffered hepato-renal failure in December 1981. When Oraflex was resumed at a lower dose of 800 mg/day on February 2, 1982, the patient again experienced hepato-renal failure.[25]

[19] See 21 C.F.R. 312(a)(1)(6).
[20] Hearings, pages 86-87.
[21] Ibid., page 87.
[22] Hearings, page 63. Oraflex's chemical similarity to Flexin, a drug approved for the relief of skeletal muscle spasm, should have alerted FDA to its potential liver toxicity. FDA removed Flexin from the market on October 13, 1961, because of a number of reports of serious and sometimes fatal liver disorders associated with its use. Both Oraflex and Flexin contained a benzoxazole nucleus. The committee is aware of only one other drug approved by FDA with this chemical feature. FDA's review of Flexin is recounted in subcommittee hearings held in 1964. See Hearings before a Subcommittee of the Committee on Government Operations, House of Representatives, "Drug Safety (Part 2)," April 28, 1964, pages 565-676.
[23] Hearings, pages 575-578.
[24] Hearings, pages 633-636.
[25] Hearings, pages 638-640.

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Another case of combined liver and kidney disease occurred during the Oraflex clinical trails, although Lilly did not completely report it to FDA until a July 2, 1982, weekly adverse experience report to the Oraflex NDA, more than ten weeks after FDA approved the drug. According to that report, a 65-year-old female Oraflex clinical trial patient was hospitalized on December 21, 1981, with hepatitis and renal failure.[26] However, a January 6, 1982, initial report to the IND, the only Lilly submission on this patient prior to the drug's approval, discussed only renal failure with an unknown relationship to Oraflex and made no mention of hepatitis or any liver disorders.[27] Yet according to its July 2, 1982, NDA submission, the company had received all paperwork concerning this patient on February 23, 1982,[28] almost two months before Oraflex was approved.

FDA's failure prior to approving Oraflex to note the association in clinical trials between the drug and serious liver disease proved particularly unfortunate in light of numerous reports of fatal and non-fatal cases of Oraflex-associated liver failure which surfaced after FDA approval.[29] Had FDA made a thorough review of all submissions to the Oraflex IND, it would have detected the drug's association with liver disease before, rather than after, it permitted marketing of the drug.

Many of the post-market reports of serious Oraflex-associated injury and death involved patients who experienced both kidney and liver failure.[30] Clearly, information on Oraflex's association with kidney disease, as well as its link to liver disease, was available in FDA files before the agency approved the drug. Despite this, Lilly proposed and FDA approved labeling which denied altogether the existence of "evidence * * * of renal [kidney] toxicity in [the Oraflex] clinical studies." [31]

Lilly had prominently reported to the Oraflex IND a total of six cases of drug-associated kidney disease prior to the drug's approval. In addition to the four reports of combined kidney and liver disease already discussed, two other reports were submitted to the Oraflex IND of drug-associated kidney disorders which had occurred during the clinical trials.

An adverse drug experience report contained in a September 17, 1981, IND submission discussed a 60-year-old male with no history of renal problems who was diagnosed as suffering from nephrotic syndrome, a kidney ailment.[32] A November 18, 1981, submission contained a follow-up report on this patient which diagnosed the case as "probable nephrotic syndrome." [33] According to a consultation notation included in this submission, "renal disease in this man is probably secondary to benoxaprofen." [34]

An August 21, 1980, IND submission described a 58-year-old woman who developed kidney complications in the form of interstitial nephritis and membranous glomerulopathy [35] while taking Oraflex. Essentially the same information was reported to the IND in a December 1, 1980,[36] follow-up submission. The case reports submitted by the clinical investigator for this patient described her condition as "drug-induced interstitial nephritis." [37] This finding was later highlighted in an FDA report of a special inspection of this investigator's records which was conducted in May 1981 at the request of FDA's Division of Scientific Investigations. According to that report, a kidney biopsy revealed the patient had "developed interstitial nephritis which was felt by the clinical investigator to be drug induced." [38]

Despite all the agency attention focused on this case of "drug-induced" kidney disease, FDA allowed Lilly to label "interstitial nephritis" as an experienced side effect whose "causal relationship" with the drug was "unknown." [39]

This case brings to six the number of prominently reported cases of drug-associated kidney disease which had occurred during the Oraflex clinical trials. The Oraflex labeling which denied evidence of such disease was not only inconsistent "with the facts as known to Lilly," [40] but also contradicted information submitted to the Oraflex IND. FDA was no more justified in approving such labeling than Lilly was in proposing it.

As discussed below,[41] the subcommittee learned that Lilly did not inform FDA of several benoxaprofen-associated deaths in the United Kingdom which one of Lilly's foreign divisions knew about months before April 19, 1982, the day FDA approved the drug.

In view of this information, the subcommittee wrote FDA Commissioner Hayes on September 20, 1982, inquiring whether the sponsor reported to FDA any other benoxaprofen-associated deaths outside the United States prior to April 19, 1982.[42] In a September 28, 1982, reply, Robert C. Wetherell, Jr., Associate Commissioner for Legislation and Information, advised the subcommittee that FDA was still reviewing its records to determine whether the company might have reported additional Oraflex-associated deaths prior to the drug's approval: "Our National Center for Drugs and Biologics informs me that additional deaths may have been reported and we are now in the process of reviewing our records, including reprints of the literature which may have been submitted by Eli Lilly and Company." [43]

That FDA did not know more than five months after approval whether the sponsor had reported Oraflex-associated deaths before approval indicates that the agency had not thoroughly examined the sponsor's IND and NDA submissions before approving the drug

[26] Hearings, page 651.
[27] Hearings, pages 630-632.
[28] Hearings, page 648.
[29] See Section VI below.
[30] Ibid.
[31] Hearings, page 110.
[32] Hearings, pages 617-619.
[33] Hearings, pages 620-622.
[34] Hearings, page 626.
[35] Hearings, pages 590-591.
[36] Hearings, pages 594-595.
[37] Hearings, page 593.
[38] Hearings, page 596.
[39] Hearings, page 110. FDA's acknowledgement of the possibility that a case of interstitial nephritis occurring in the Oraflex clinical trials might have been drug-related is itself, as Dr. Alan Lisook of FDA's Division of Scientific Investigations observed, inconsistent with its original approval of labeling disclaiming existence of "evidence * * * of renal [kidney] toxicity in clinical studies." See Hearings, pages 614-615.
[40] Hearings, pages 614-615.
[41] See Section VI below.
[42] Hearings, page 544.

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for marketing. FDA's lack of information on reports of Oraflex-associated deaths is all the more surprising because FDA Commissioner Hayes testified in his August 3 appearance before the subcommittee that the agency was conducting an intensive investigation of alleged adverse reaction reporting violations by Lilly in connection with Oraflex and several other investigational and marketed drugs.[44]

Due to a filing backlog in the documents room of the division charged with reviewing the Oraflex NDA, FDA was unable to determine whether the sponsor had reported all significant adverse reactions in the several months immediately preceding the drug's approval on April 19, 1982. As of July 2, 1982, more than two months after the drug was approved, only those reactions reported by Lilly prior to December 2, 1981, had been entered into that division's filing system and were thus reviewable.[45] Those adverse reactions which Lilly reported after that date completely escaped the notice of FDA's reviewers. Included among these adverse reactions were three of the four cases of combined liver and kidney diseases which were reported before approval.

As of the subcommittee's August 3 hearing—three and one half months after Oraflex was approved—FDA still was unable to verify the company's claim that it had reported serious drug-associated adverse effects to the agency prior to the drug's approval. Initially, the company disclaimed the existence of jaundice—a serious liver disorder—in the Oraflex clinical trials. Two Lilly vice-presidents—one in a letter in the May 29, 1982, British Medical Journal [46] and the other in a May 14, 1982, phone conversation with Dr. Robert Temple of FDA's Office of New Drug Evaluation [47]—stated that no Oraflex clinical trial patients had developed jaundice. Then, at a June 23, 1982, meeting, Lilly officials told FDA that they had discovered five cases of jaundice in the clinical trials, two of which had been submitted to the NDA and three of which were part of the firm's "unprocessed" and unreported IND data.[48] According to a memorandum of that meeting, FDA officials "expressed surprise that cases of jaundice had not been submitted prominently to the NDA prior to its approval." [49] Dr. Robert Temple, Acting Director, FDA's Office of New Drug Evaluation, testified before the subcommittee, however, that the memorandum of the June 23, 1982, meeting was "not accurate." [50] Lilly later informed FDA that only four cases of hepatic disease occurred prior to approval,[51] all of which, Dr. Temple told the subcommittee, he thought "were reported in one way or another to something." [52] As late as the subcommittee's

[44] Hearings, page 234.
[45] Hearings, page 119.
[46] Hearings, page 105.
[47] Hearings, page 107.
[48] Hearings, page 111.
[49] Ibid. At this meeting, Lilly neglected to mention that many of the patients who developed jaundice, as previously discussed, also experienced kidney failure. Since the "meeting was scheduled as a result of the liver and renal toxicity problems reported since the approval of Oraflex on April 19, 1982," (hearings, page 112) such a disclosure would have been appropriate.
[50] Hearings, page 114.
[51] Ibid. Actually, a fifth case of hepatic disease occurred prior to approval but was reported to FDA by the clinical investigator on April 28, 1982, after the drug was approved. Hearings, page 642.
[52] Ibid.

August 3 hearing, FDA had still not confirmed Lilly's discrepant versions of what adverse reactions had been reported. In fact, FDA was unable to confirm whether Lilly had reported several Oraflex-associated liver reactions prior to the drug's approval.[53]

B. PRIOR TO APPROVING ORAFLEX, FDA MADE NO EFFORT TO OBTAIN INFORMATION ON ITS SAFETY FROM FOREIGN COUNTRIES IN WHICH IT WAS ALREADY MARKETED

The law prohibits FDA from approving a new drug for marketing unless it has sufficient information that it is safe for its intended use. In this connection, FDA has the responsibility to inform itself of all known adverse effects associated with such a drug, and to make full use of such information in weighing the drug's risks against its purported benefits. FDA approved Oraflex without meeting that standard.

A February 1982 adverse reaction register on Oraflex prepared by the Committee on Safety of Medicines (CSM) in the United Kingdom showed 27 benoxaprofen (Oraflex)-associated deaths in the U.K., including 15 deaths from gastrointestinal disorders, three deaths from kidney and two deaths from liver disease. In addition the register showed 25 reports of non-fatal liver and nine reports of non-fatal kidney disease among the drug's users in the United Kingdom. Dr. John P. Griffin, Professional Head of the Medicine Division of the CSM, sent the register unsolicited to FDA on May 20, 1982, approximately one month after the FDA approved Oraflex.[54] Some or all of this information might have been available to FDA prior to its April 19, 1982, approval of Oraflex had the agency taken the initiative to inform itself of the British experience with the drug.

In the 10 months prior to March 1982, Danish health authorities had received 101 benoxaprofen-associated adverse effect reports covering 143 reactions, three of which were fatal.[55] Two of the three Danish deaths involved liver disease. This information, too, might have been available to FDA prior to its approval of the drug.

FDA has no established procedures for obtaining foreign adverse reaction data for drugs under investigation in the United States which are already marketed in other countries. The committee believes FDA should make full use of the marketing experience in other nations with drugs that are under NDA review, particularly since pre-marketing studies often do not include a sufficient number of patients to detect unanticipated and relatively infrequent adverse reactions. In short, the limitations of clinical testing for predicting the full range and severity of a new drug's adverse effects under normal conditions of medical practice intensifies the need for seeking adverse reaction data from all possible sources. The commercial marketing of new drugs in foreign countries obviously is an important source of this information.

FDA Commissioner Hayes maintained in testimony before the subcommittee that FDA's "files would literally explode" were

[53] Hearings, page 127.
[54] Hearings, page 120. Letter and register on file in subcommittee office.
[55] Asgar Pedersen, Vgeskr Laeger, June 7, 1982, pages 1704-1705. Available in subcommittee files.

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agency "to solicit all adverse reactions on all drugs from all countries that have such information." [56] The committee does not believe the evidence supports this conclusion. For example, the two adverse reaction registries which the United Kingdom Committee on Safety of Medicines sent to FDA for benoxaprofen consisted only of a total of six pages of tabular data.[57] Moreover, it is essential that FDA have all available adverse reaction data for a new drug if it is to make a balanced and reliable risks-to-benefit judgment.

Even tabular data, which do not include detailed reports on patients experiencing adverse effects, might prove valuable to FDA. The June 1982 benoxaprofen registry, which the Committee on Safety of Medicines sent to FDA, disclosed 256 reports of gastrointestinal disorders, 19 of which involved fatalities. In a memorandum of a July 7, 1982, telephone conversation, Dr. Robert Temple, Acting Director of FDA's Office of New Drug Evaluation, discussed the significance of this information:

> What is most impressive in that printout is the number and severity of gastrointestinal disease with what appear to be a surprisingly large number of cases of G.I. hemorrhage and perforation resulting in death. * * * There are about 20 reports of death related to gastrointestinal hemorrhage, perforation, etc. for a frequency of about 1 in 25,000 users. If we assume some reasonable level of underreporting such as a 20 percent reporting rate, we would calculate a fatality rate of about 1 in 5,000, a figure that, offhand, seems quite high, even for non-steroidal anti-inflammatory drugs, which are known to cause gastrointestinal bleeding, and hemorrhage, some episodes of which naturally will be fatal.[58]

Prior to studying these data, FDA was unaware of the drug's association with an exceptionally large number of deaths from gastrointestinal disorders. Foreign marketing data, even in tabular form, can provide FDA with an indispensable source of information on the types and frequency of serious side effects reported for new drugs under investigation in the United States.

VI. Lilly Did Not Report Serious Oraflex-Associated Adverse Reactions and Thereby Prevented FDA From Fully Assessing the Drug's Risks Prior to Its Approval

FDA regulations require sponsors to supply the agency with prompt and full reports of "any finding" associated with a new drug under investigation "that may suggest significant hazards, contraindications, side effects, and precautions pertinent to the safety of the drug." [59]

An October 5, 1982, internal Lilly memorandum reveals that, prior to the drug's approval on April 19, 1982, the firm failed to report to FDA 32 benoxaprofen-associated deaths outside the United States known to the company, including its foreign affiliates.[60] Eleven (34.4 percent) of these deaths involved liver and ten (31.3 percent) kidney disease. Six (18.8 percent) of these deaths, in fact, showed both liver and kidney involvement.[61] In addition, ten (31.3 percent) were associated with gastrointestinal disorders.[62] Aplastic anemia was also implicated in three (9.4 percent) of the unreported deaths.[63] The list of drug-associated adverse reactions in the original Oraflex package insert did not include aplastic anemia.

The committee believes that Eli Lilly and Co. was responsible under the law, for making prompt, complete, and accurate reports to FDA of all significant Oraflex-related adverse reactions known to the firm's foreign affiliates. In this connection, the Supreme Court has ruled that the Food, Drug, and Cosmetic Act "imposes not only a positive duty to seek out and remedy violations but also and primarily, a duty to implement measures that will insure that violations will not occur. The requirements of foresight and vigilance imposed on responsible corporate agents are . . . no more stringent than the public has a right to expect of those who voluntarily assume positions of authority in business enterprises whose services and products affect the health and well-being of the public that supports them." [64]

An internal Lilly memorandum shows that one official in the firm's Indianapolis headquarters was aware of seven of these deaths before the FDA approval date. Four of those deaths involved kidney and five gastrointestinal disease. One of the four kidney cases also involved liver failure.[65]

The company memorandum lists two colleagues of this Lilly official as knowing of five of the seven unreported deaths prior to the drug's approval.[66] One of these colleagues, in fact, has admitted pre-approval knowledge of 29 Oraflex-associated deaths outside the United States.[67] One of these deaths was reported to FDA before

[56] Hearings, page 121.
[57] One registry consisted of two pages; the other of four pages.
[58] On file in subcommittee office.
[59] 21 CFR 8.312 (a)(6).

[60] Memorandum in subcommittee files. An FDA inspection begun on October 18, 1982, which was designed to determine when Lilly reported Oraflex-associated deaths outside the United States to the FDA, did not turn up this memorandum. FDA inspectors were only able to document 25 unreported deaths known by "Eli Lilly and Company and/or its divisions, subsidiaries or affiliates prior to the NDA approval date." Establishment Inspection Report, November 1982, page 28. In subcommittee files.
[61] Calculations based on information in Exhibit A, Establishment Inspection Report, November 29, 1982. In subcommittee files. Adverse reaction information on one of the 32 deaths could not be located.
[62] Ibid.
[63] Ibid.
[64] *United States* v. *Park*, 421 U.S. 658, 672 (1974).
[65] The October 5, 1982, memorandum is in subcommittee files. The calculations are based on information in Exhibit A, Establishment Inspection Report, November 29, 1982, which is also in subcommittee files. This official learned of two of these deaths, including one associated with hepato-renal failure, as early as October 1981, one-half year before Oraflex was approved.
Because they did not obtain the October 5, 1982, memorandum, FDA personnel who inspected Lilly's Oraflex records from October 18 to November 19, 1982, could only document a total of five unreported deaths known to Lilly's Indianapolis officials prior to the drug's approval. The total was based on a report from Europe for the last quarter of 1981 which was sent to these such officials. One copy of the report showed its receipt by Lilly's Indianapolis headquarters on January 27, 1982, almost three months before Oraflex was approved. Other reactions listed in the fourth quarter 1981 report—among them obstructive airways disease, deterioration of filming alveotitis, and vasculitis—were not previously known to FDA. See Exhibit T-3, Establishment Inspection Report, November 29, 1982, pages 4-5.
[66] See the October 5, 1982, Lilly memorandum in subcommittee files.
[67] Deposition of Dr. W. I. H. Shedden in *Borom* v. *Eli Lilly and Company*, Civil Action Number 83-38-COL. (M.D. Ga.), June 21, 1983. In subcommittee files.

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the drug's approval.[68] Twenty-five of these deaths were listed in a January 1982 benoxaprofen adverse reaction registry provided by the British Committee on Safety of Medicines.[69] Eighteen of these British deaths involved gastrointestinal disorders, two liver disease, and two kidney aliments.[70] Three additional unreported deaths were discussed in a pre-publication copy of an article [71] reporting drug-associated adverse reactions occurring in Denmark, two involving liver dysfunction and one Stevens Johnson syndrome, a serious skin disease.[72]

Other Lilly officials in Indianapolis were reportedly advised, prior to Oraflex's approval, of these unreported deaths, including the president of Lilly Research Laboratories, the head of Lilly's Regulatory Affairs Division, and the monitor for the Oraflex clinical trials in the United States.[73]

Documented receipt of some of this information by Lilly's U.S. personnel, FDA personnel have noted, contrasted with a Lilly vice president's statement during a November 19, 1982, conference with agency representatives that U.S. officials of Lilly "had not been aware of liver or kidney problems" until well after the drug had been approved.[74]

Despite FDA's requirement that it receive prompt and full reports of "any finding" associated with an investigational new drug which may significantly relate to that drug's safety,[75] one senior FDA official has expressed the belief that sponsors are not routinely reporting to FDA deaths and other significant adverse experiences associated with the foreign marketing of drugs under investigation in the United States and that Lilly's failure to make such reports was probably consistent with current industry practice.[76] In a similar vein, the Group Leader for the Oraflex review has stated that "I do not see anything outside the range of normal in Lilly's behavior as compared with the other companies whose

[68] Lilly reported a West German death, which involved a patient who developed toxic epidermal necrolysis (Lyell's syndrome), a serious dermatological condition. Such a death was reported to the Oraflex IND on June 29, 1981. Hearings, page 548. This case was forwarded to Lilly's Indianapolis headquarters by its affiliate in the United Kingdom, which in turn received it from Lilly's West German affiliate. See Establishment Inspection Report, November 29, 1982, page 15. A section of the originally approved Oraflex labeling which acknowledges reports "from marketing outside the United States" includes toxic epidermal necrolysis as a reaction which has been associated with use of the drug. See Hearings, page 110.

[69] The Committee on Safety of Medicines periodically makes available to pharmaceutical manufacturers in the U.K. registries of reported adverse effects associated with drugs they are licensed to sell. See "Data in Printouts from the Adverse Reactions Register" published by the Committee on Safety of Medicines in Murch 1982. This document is available in subcommittee files. Lilly's British affiliate had obtained from the Committee on Safety of Medicines benoxaprofen adverse reaction printouts in February 1981, April 1981, May 1981, and January 1982. Exhibit J., page 1, Establishment Inspection Report, November 29, 1982. Available in subcommittee files. The April 1981 registry showed one death (from a perforated gastric ulcer), and the May 1981 registry 3 deaths (all from gastrointestinal disorders). Ibid., pages 13 and 19.

[70] See Exhibit J, Establishment Inspection Report, November 29, 1982, pages 11-12. In subcommittee files.

[71] Asgar Pedersen, Vgeskr Laeger, June 7, 1982, pages 1704-5. In subcommittee files.

[72] Deposition of Dr. Shedden, June 21, 1983. In subcommittee files.

[73] Deposition of W.I.H. Shedden in *Domiano* v. *Eli Lilly and Company*, Civil Action No. 82-0982 (M.D.Pa.), June 29, 1982, page 48. In subcommittee files.

[74] Establishment Inspection Report, November 29, 1982, page 24. Nothing in the Oraflex labeling reflected knowledge of kidney involvement in the deaths of patients taking the drug. In fact, the only discussion of drug-associated kidney disease in that labeling was a denial of evidence of kidney toxicity in the Oraflex clincial trials. See Section V.A.1. above.

[75] 21 CFR § 312.1(a)(6).

[76] The memorandum of the October 14, 1982, FDA conference at which this opinion was expressed is in the subcommittee files.

NDAs I reviewed . . . or as compared with the broader spectrum NDAs I have seen but have not formally surveyed." [77]

The committee finds this view of law enforcement wholly indefensible. As discussed subsequently in this report, FDA has a clear responsibility for instituting effective policies and procedures to insure that it is promptly informed of all known deaths and serious adverse effects associated with investigational new drugs, wherever they may occur. FDA's regulations require that "any" significant finding relevant to the safety of an investigational drug be promptly reported to the agency. The committee believes it essential that FDA receive all such information if it is to carry out its statutory responsibility for protecting the public from unsafe drugs. In this connection, it should be remembered that the thalidomide disaster was averted in the United States largely because of reports of birth defects associated with the use of thalidomide in other countries which, unlike the United States, had approved it for marketing.

When FDA initiated an inspection of Lilly's Oraflex records in October 18, 1982, FDA had before it a year-old recommendation for the prosecution of those Lilly officials responsible for failing to report "important adverse findings" about Oraflex and several other marketed or investigational drugs. In a September 29, 1982 memorandum, Dr. Michael J. Hensley, a medical officer with FDA's Division of Scientific Investigations, made this recommendation after alleging, based on a previous inspection of the company's records, that Lilly had failed to report 81 of the 173 Oraflex-associated adverse effects which were submitted to the company's management by five clincial investigators. Sixty-five of these 81 adverse effects were eventually confirmed as Oraflex-related.[78]

FDA's inspection of Lilly's Oraflex records in October and November of 1982 actually represented the seventh establishment inspection it had conducted of the firm over the previous three years. After receiving allegations from a former Lilly employee that the firm had withheld significant information from FDA,[79] the agency undertook a major investigation in the fall of 1979 which eventually uncovered evidence of serious omissions and deficiencies in Lilly's reporting to FDA of important findings in connection with several investigational [80] and marketed [81] drugs. In view of the evidence, Dr. Marion J. Finkel, then the Associate Director for New Drug Evaluation, advised Lilly in a March 12, 1982, letter

[77] "Additional Views," Findings, Conclusions, and Recommendations of the Eli Lilly and Company Task Force, March 1983, page 64.

[78] Hearings, page 90. Despite testimony before the subcommittee by Dr. Robert T. Acting Director of FDA's Office of New Drug Evaluation, that Lilly's failure to report these actions did not violate agency regulations (Hearings, page 92), FDA recently acknowledged such nonreporting "may have been an attempt to bias the safety profile of the drug." (Findings, Conclusions, and Recommendations of the Eli Lilly and Company Task Force, March 1983.)

[79] Hearings, page 128.

[80] FDA personnel found serious irregularities in Lilly's reporting for several investigational new drugs besides Oraflex, including two anti-arrhythmic drugs—aprindine (pages 128-660-673 of the Hearings) and drobuline (pages 169-192 and 674-681 of Hearings) and perhaps drug for breast cancer (pages 285-287 of Hearings).

[81] FDA investigators have concluded that Lilly failed to make required reports of adverse actions associated with monensin, an approved animal feed supplement (pages 192-219 of Hearings). They also found that Lilly did not report cardiotoxicity findings from dog experiments involving Darvon, an approved analgesic (pages 249-280).

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FDA's concerns about the timeliness, accuracy, and completeness of the firm's submissions.[82]

At the subcommittee's August 3, 1982, hearing, FDA officials characterized the investigation of Lilly's reporting practices as "full-fledged" [83] and "ongoing." [84] Despite this, the agency did not undertake an inspection of Lilly's report files concerning Oraflex-associated deaths outside the United States until after it had been informed by the subcommittee that the company had failed to report 13 such deaths to FDA prior to the agency's approval of the drug on April 19, 1982. Based solely on the findings of this inspection, which uncovered additional unreported Oraflex-associated deaths,[85] FDA requested on April 20, 1983, that the Justice Department initiate a grand jury investigation.[86]

The United Kingdom's Committee on Safety of Medicines informed the subcommittee in an August 24, 1982, response to the subcommittee's letter of August 11, 1982,[87] that Dista Products Ltd., a wholly-owned Lilly company, had reported at least eight deaths associated with use of benoxaprofen in the United Kingdom prior to April 19, 1982, the day FDA approved the drug.[88] The last of these deaths was reported to the British Committee on January 15, 1982, more than three months before FDA's approval for marketing in the United States. The subcommittee advised FDA of its findings concerning the eight benoxaprofen-associated deaths on September 7, 1982.[89] In a subsequent response to a subcommittee inquiry, FDA Commissioner Hayes wrote that these deaths were not reported to FDA prior to NDA approval, a fact which Lilly had confirmed during a recent phone call.[90]

A further exchange of correspondence between the subcommittee and the British Committee on Safety of Medicines elicited the information that three of the eight deaths involved gastrointestinal disorders (1 gastric ulcer hemorrhage, 1 perforated gastric ulcer and 1 case of melena), two involved kidney disease (1 case of uremia and 1 case of nephritis) and one primarily involved liver disease (1 case of hepatic failure accompanied by renal failure).[91] These are the same fatal side effects which apparently led to Lilly's decision on August 4, 1982, to suspend further sale of Oraflex worldwide.

In view of the company's failure to report eight deaths, the subcommittee asked FDA on September 20, 1982, whether the compa-

[82] Hearings, pages 230-233.
[83] Hearings, page 230.
[84] Hearings, page 228.
[85] FDA inspectors documented a total of 25 unreported deaths prior to approval of the drug. Establishment Inspection Report, November 29, 1982, page 28. In subcommittee files.
[86] Letter from Thomas Scarlett, Assistant General Counsel, Office of the General Counsel, Food and Drug Division, Department of Health and Human Services, to J. Patrick Glynn, Director, Office of Consumer Litigation, Civil Division, Department of Justice. FDA confined this request to Lilly's reporting of Oraflex-associated adverse reactions and did not ask the Justice Department to investigate Lilly's alleged failure to report adverse effects for other drugs.
FDA believed that a grand jury investigation was necessary to determine whether Lilly officials had violated criminal provisions of 18 U.S.C. § 1001 by intentionally scheming to conceal important information from the agency, or the provisions of § 303(b) of the Food, Drug, and Cosmetic Act by intending to defraud or mislead the agency.
[87] Hearings, page 528.
[88] Hearings, page 529.
[89] Hearings, pages 530-531.
[90] Hearings, page 532.
[91] Hearings, page 533.

ny had reported to FDA any other benoxaprofen-associated death outside the United States prior to April 19, 1982.[92] FDA's Octobe 12, 1982, response based on information furnished by Lilly in recent phone conversation,[93] omitted mention of five other benoxa profen-associated deaths which the subcommittee learned had bee reported before April 19, 1982, to Dista Products Ltd., Lilly's Bri ish subsidiary. All of these were reported to Dista by Dr. Hug McA Taggart of the Department of Geriatric Medicine, Belfast Cit Hospital, Belfast, Northern Ireland. Dr. Taggart had submitted r ports to Dista on February 9, 1982, of the deaths of two elderl women taking the drug from jaundice and renal failure.[94] O April 7, 1982, Dr. Taggart submitted reports on three addition deaths of elderly women taking benoxaprofen. Two of these cas involved jaundice in conjunction with renal failure and one jau dice alone.[95]

In addition, Dr. Taggart, in a September 10, 1982, letter to t subcommittee, stated that at a March 16, 1982, benoxaprofen pr motional meeting in Belfast, he "had a detailed conversation wi a member of the medical staff of Dista in the presence of a c league in which I gave general details of the five cases and indic ed my intention to submit these for publication." [96] In a conver tion with the subcommittee staff, Dr. Taggart identified this Dis employee as Dista's medical director.[97] Lilly records in Indianap lis list this Dista official as a Lilly employee—Medical Direct Pharmaceutical Marketing, Eli Lilly and Company Ltd. in Basi stoke, Hampshire.[98]

Lilly did not officially notify FDA of these deaths until a May 1982, submission to the Oraflex NDA,[99] several weeks after O flex was approved and only after the five cases were reported Dr. Taggart and Dr. Joan M. Alderdice in an article entitl "Fatal Cholestatic Jaundice in Elderly Patients Taking Benoxap fen" in the May 8, 1982, issue of the British Medical Journal. T was the first article in the medical literature linking the drug w fatal liver and kidney disease. Lilly's May 17, 1982, NDA subn sion enclosed this and two other articles on adverse effects assoc ed with use of the drug.[100]

FDA eventually became extremely concerned, as Dr. Rob Temple testified before the subcommittee, with the "peculiar" fa combination of drug-associated liver and kidney disease descri in this and similar published reports from Great Britain.[101] fact, according to FDA, such reports contributed to the eventual cision to remove the drug from the market. In a form letter

[92] Hearings, page 544.
[93] Memorandum of this October 1, 1982, conversation is in the subcommittee files.
[94] Hearings, page 538-540.
[95] Hearings, page 541-543.
[96] Hearings, page 538.
[97] Hearings, page 536.
[98] Establishment Inspection Report, November 29, 1982, Exhibit D, page 2.
[99] Hearings, pages 552 and 554. Lilly informally notified Dr. John Crotti of FDA of deaths on May 7, 1982. Dr. Crotti's May 10, 1982, memorandum of this contact is in the sul mittee files. Lilly also told Dr. Robert Temple, Acting Director, Office of New Drug Evalu of these deaths in a May 14, 1982, telephone conversation. Hearings, page 108.
[100] Hearings, page 554.
[101] Hearings, page 95.

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sponding to Congressional requests for an explanation for that withdrawal, FDA wrote:

> Shortly after Oraflex's approval in the United States on April 19, 1982, there appeared in the British medical literature a number of reports of deaths in elderly patients from liver and kidney failure * * * [I]t appears likely the drug was responsible for at least some of the British deaths and may have an unusual ability to cause simultaneous liver and kidney damage.[102]

"Of particular concern" to FDA, wrote Dr. John Harter, Group Leader in FDA's Oraflex review, immediately following the drug's removal from the U.S. market were the "hepatic +/– renal reactions resulting in death." [103]

According to an October 7, 1983, submission by Lilly to the Oraflex NDA, 215 hepatic and/or renal events, including 36 deaths, have been associated with Oraflex in the United States from the time it was approved until October 5, 1983.[104]

Prior to Lilly's suspension of Oraflex sales, the publication of Dr. Taggart's findings was instrumental in forcing post-market modifications in the Oraflex labeling. The vice president of Lilly Research Laboratories has stated that Lilly proposed in May 1982 to reflect Dr. Taggart's experience in revised labeling which mentioned reports of death from drug-associated liver disease.[105]

Following a June 3-4, 1982, Arthritis Advisory Committee meeting on the liver toxicity of nonsteroidal anti-inflammatory drugs, in which those findings were discussed at length, FDA required Lilly to revise the Oraflex labeling to include the following new language:

> Severe hepatic reactions, including cholestatic jaundice and cases of fatal hepatitis associated with renal failure, have been reported with benoxaprofen. * * * In elderly patients, renal function as assessed by creatinine clearance is normally decreased and serum creatinine levels alone may not accurately reflect a decrease in renal function. If data from a creatinine clearance test are not available, therapy in the elderly should generally be initiated using one-half to two-thirds of the usual dose (i.e., 300-400 mg daily).[106]

"[R]eported fatalities in the elderly women in England," Dr. Harry Meyer, Director, National Center for Drugs and Bilogics, testified before the subcommittee, led FDA to conclude that "it would be safer to call for reduced dosages of the drugs. That, in fact, has been incorporated in the labeling." [107]

Lilly issued a June 29, 1982, Dear Doctor letter which, in explaining the new Oraflex dosage schedule, stated: "Recent reports in British medical publications have linked Oraflex to cases of hepatic

[102] Document in subcommittee files.
[103] His August 5, 1982, Bureau of Drugs Hazard Evaluation Criterion for Human Drug Recalls is in subcommittee files.
[104] Document in subcommittee files.
[105] Deposition of W.I.H. Shedden in *Domiano* v. *Eli Lilly and Company*, Civil Action No. 82-0982 (M.D.Pa.), June 29, 1982, page 70. In subcommittee files.
[106] Revised Oraflex labeling dated June 24, 1982.
[107] Hearings, pages 118-119.

dysfunction, frequently associated with acute renal failure. * * Data in these reports are incomplete, but the information availab suggests that the adverse effects may be drug related. * * * The events occurred primarily in elderly female patients who receive full 600 mg daily doses of the drug." [108] Lilly did not, as one of i vice presidents claimed at a November 19, 1982, meeting with FD officials, first learn of the drug's association with fatal liver ar kidney disease when Dr. Taggart's article was published appro mately two and one-half weeks after FDA approved the drug.[1 Dr. Taggart, in fact, had informed the company of such an asso ation more than two months before FDA approved Oraflex. Lilly failure to report Dr. Taggart's findings promptly to FDA depriv the agency of information that was important for a responsible a sessment of the risks of Oraflex before the drug was allowed on t American market.

VII. FDA Enforcement of its Adverse Reaction Reporting Requirements was Inadequate

Shortly after FDA discovered unreported Oraflex deaths by specting Lilly records in late 1982, the Oraflex Group Leader fou that Pfizer Pharmaceuticals had also failed to report to FDA least 26 "serious adverse reactions associated with use of its arth tis drug Feldene outside the United States" prior to the drug's proval on April 6, 1982.[110] The reactions involved several sev episodes of gastrointestinal bleeding, including one death.[111]

The subcommittee devoted most of its hearing on August 4, 19 to FDA's approval of Feldene.[112]

In a December 9, 1982, letter to Pfizer, the Director of the D sion of Oncology and Radiopharmaceutical Drug Products wr "We feel such reports should have been available as a minimum Pfizer's U.S. physicians and optimally to FDA reviewers as v during the deliberations about Feldene safety and adverse react labeling." [113]

The subcommittee brought this matter to the attention of ser FDA managers at an April 27, 1983, hearing, more than months after an agency medical officer uncovered the unrepo Feldene reactions.[114] Three months after this hearing, FDA

[108] Letter in subcommittee files.
[109] See page 4 of the memorandum of that meeting which appears in the November 29, Establishment Inspection Report, as Attachment A. Document in subcommittee files.
[110] Hearings before a subcommittee of the Committee on Government Operations, Hou Representatives, "FDA's Regulation of Zomax," April 27, 1983, page 440.
[111] Case summaries of the unreported adverse reactions are in subcommittee files.
[112] Hearings, pages 367 to 450.
[113] "FDA's Regulation of Zomax," page 440. In a February 7, 1983, letter to Dr. Willi Gyurfas, Director, Division of Oncology and Radiopharmaceutical Drug Products, Pfizer a that none of the unreported reactions were "unexpected as defined in 21 CFR § 310.300(b)(that they further confirm that the side effect profile of Feldene is consistent with that ci the product labeling." The committee notes that the relevant reporting requirement in th stance is 21 CFR § 312.1(a)(6), which applies to drugs under investigation and not, as Pfize gests, 21 CFR § 310.300(b)(2), which applies to approved drugs. Under 21 CFR § 312.1(a)(6 significant findings pertinent to the safety of an investigational drug, whether or not "une ed," must be promptly reported to FDA.
In addition, FDA has concluded that under 21 CFR § 312.1(a)(6) "an (adverse drug react required to be reported to FDA regardless of whether it is * * * already reflected in the la of the product." Findings, Conclusions and Recommendations of the Eli Lilly and Compan Force, March 1983, page 3.
[114] The medical officer wrote about his discovery of the unreported reactions on Novem 1982. See "FDA's Regulation of Zomax," page 441.

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cials concluded that, had Pfizer promptly reported the reactions, the original Feldene labeling might "have been stronger." [115] The labeling might have reported the drug's association with gastric perforation [116] and, according to agency reviewers, might have resembled the September 1982 revisions made in the warning section of the Feldene package insert which discussed reports of "severe" and sometimes "fatal" drug-associated adverse effects.[117]

This bears a strong resemblance to the Oraflex situation. Pfizer did not inform FDA of serious adverse reactions which apparently were reported to its foreign divisions prior to FDA's approval of Feldene. However, no referral of the Pfizer matter was made to any investigative arm of the FDA.[118]

The committee questions FDA's commitment to enforcing its requirement that it promptly receive reports of "any" significant finding associated with the safety of a new drug under investigation. In this connection, the committee notes that FDA did not investigate the extent of Lilly's failure to report Oraflex-associated deaths outside the United States until after it had been advised by the subcommittee of 13 such unreported deaths.[119]

The FDA is charged with executing the Food, Drug, and Cosmetic Act and its implementing regulations. The committee believes FDA places the public's health at risk when it does not vigorously enforce the legal requirement that a sponsor report all significant adverse reactions to a new drug under clinical investigation, since this information is needed to weigh the risks of the drug against its potential benefits.

[115] August 4, 1983, memorandum from Dr. Robert Temple, Acting Director, Office of New Drug Evaluation and Dr. John Harter, Medical Officer, Division of Oncology and Radiopharmaceutical Drug Products, to Mr. Joseph P. Hile, Associate Commissioner for Regulatory Affairs, page 3. In subcommittee files.

[116] Gastric perforation was included among the unreported adverse effects. Ibid., page 1. At FDA's request in October 1983, perforation was added to the list of adverse reactions in the Feldene labeling, the change being made in December 1982.

[117] Ibid., pages 2-3.

[118] "FDA's Regulation of Zomax," page 443.

[119] FDA advised the subcommittee of its decision to undertake such an investigation after learning from the subcommittee of 8 unreported deaths. Hearings, pages 530-531 and 548-549. By the time FDA began its final inspection of Lilly's records, it had been advised by the subcommittee of five additional Oraflex-associated deaths which Lilly failed to report to FDA prior to

ADDITIONAL VIEWS OF HON. ROBERT S. WALKER, HON FRANK HORTON, HON. LYLE WILLIAMS, HON. WILLIAI F. CLINGER, JR., HON. RAYMOND J. McGRATH, HON DAN BURTON, HON. TOM LEWIS, HON. ALFRED A. (AI McCANDLESS, AND HON. LARRY E. CRAIG

While we can support the Committee's report, several concerı should be expressed to complete the record.

The Subcommittee hearings on which the report is based we held 15 months ago. The findings and recommendations are val but lose considerable impact as the report was not made promptl

Passage of considerable time between hearings and the issuan of this report has created another concern. No Members of tl present Subcommittee responsible for the report were Subcomm tee Members in 1982 when the hearings were convened. Tl makes it difficult for Members to contribute constructively regai ing more detailed issues in the report.

We note that since the August 1982 hearings the Food and Dr Administration (FDA) has taken constructive action to answer c cerns about the agency's Investigational New Drug/New Drug A plication (IND/NDA) adverse drug experience reporting syste Several responses should be mentioned.

First, prior to the August 1982 hearings, FDA attempted admin tratively to ensure that agency reviewers were made aware of new safety information obtained by NDA applicants before appr al decisions became final. In a July 30, 1982, memorandum fr the Acting Director, Office of New Drug Evaluation, appropri FDA staff were directed: (1) to check the corresponding IND file any adverse drug experience reports, submitted since the "da lock" point of the NDA, that might alter the approval decision cause major changes in labeling; (2) for pending NDAs to be s that IND annual reports were not unduly delayed, and that a d copy is supplied to the NDA reviewer; and (3) at pre-NDA meeti or for NDAs early in the review process, to reach explicit ag ments with NDA applicants on a safety data update plan, with filing going directly to the NDA.

Second, in the agency's proposed revisions to the new drug ap cation regulations (NDA Rewrite) published on October 19, 1 FDA proposed an explicit requirement for NDA applicants submit "safety update reports" periodically to the agency while NDA is pending with FDA for review, including a final report lowing receipt of an approvable letter.

Finally, both the NDA Rewrite proposal and the proposed ı sions to the investigational new drug application regulations (Rewrite) published on June 9, 1983, reinforce current regulator quirements for applicants to report to FDA adverse drug ex ence information, received or obtained by the applicants from source, throughout the entire IND/NDA process. Final regulat

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for both the NDA and IND Rewrites are under review within the agency.

ROBERT S. WALKER,
FRANK HORTON,
LYLE WILLIAMS,
WILLIAM F. CLINGER, Jr.,
RAYMOND J. MCGRATH,
DAN BURTON,
TOM LEWIS,
ALFRED A. (AL) MCCANDLESS,
LARRY E. CRAIG.

ADDITIONAL VIEWS OF HON. RAYMOND J. McGRATH

I am in general agreement with the comments contained in t Subcommittee's report, and in addition, I have cosigned the vie of the Subcommittee's ranking member, Mr. Walker. However, the only sitting member of Congress who was on the subcommit and participated in the hearings on Oraflex in a substantive wa feel constrained to make some further comments.

At the outset, I must point out that the hearings which w held on August 3 and 4, 1982, were entitled "The Regulation New Drugs by the Food and Drug Administration: The New D Review Process." The only witnesses to appear at those heari were representatives of the Food and Drug Administration. How er, approximately one third of the report in question deals not w the regulatory practices of the FDA but with the research and m keting practices of the manufacturer of Oraflex, Eli Lilly and C pany. To this end, it may have been helpful for the subcommit to have heard testimony from representatives of the comp itself.

I have other concerns with the timing of the report and with information on which many of its conclusions are based.

First, the hearings were held fourteen months ago. Neither previous chairman of the subcommittee nor its previous rank member are still in Congress. Indeed, there are no current m bers of the Subcommittee on Intergovernmental Relations Human Resources who were members of that subcommittee in 1 when the hearings were held. While I have little substantive agreement with the report itself, it should be noted that this i essence a staff report, and that no members of the subcommi which issued the report actually participated in the hearings.

Second, the report contains references to numerous docume which came into the subcommittee possession after the comple of the hearing on which the report is based. Unfortunately, hearings were held subsequent to the 1982 hearings to exam new, and apparently important, documents which had come the subcommittee's possession.

Finally, I am concerned that the report presents an incomp picture of Eli Lilly and Company's actions, and of the regula efforts of the FDA. There are two specific charges which have b made which are not necessarily borne out by the facts presente the report.

For example, the report cites a 1981 FDA internal memoranc which recommends criminal prosecution of Lilly officials for in tionally failing to report certain critical adverse reaction data to FDA. Information presented at the hearing and otherwise avail to the subcommittee shows that the FDA accepted Lilly's den stration that parts of the memorandum in question were in e hence casting doubt on the validity of its conclusions.

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Specifically, statements by senior FDA officials at the hearing indicated that many of the reactions in question were relatively minor and had been encountered with sufficient frequency in clinical trails (p. 93 of the hearing record); a memorandum prepared by FDA enforcement officials stated that the adverse reactions identified by the investigator had "no effect on the labeling approvability" of the NDA (p. 240); and the March 3, 1983, report of the FDA Eli Lilly and Company Task Force repeated the FDA's view that the adverse reactions in question had no effect on review of the Oraflex NDA. I would add, too, that the company itself prepared a point-by-point rebuttal to the investigator's findings, which it submitted to the FDA on September 16, 1982. The hearing record makes no note of this document, and if it is not in the subcommittee's files, it should be, in the interests of fairness.

The second charge involves the alleged failure to report certain fatalities which occured overseas prior to the marketing of Oraflex in this country. The report refers to 21 CFR 312.1(a)(6), which requires sponsors to supply the agency with prompt and full reports of and adverse finding associated with a new drug under investigation, including foreign data. In actuality, this particular regulation has generally been interpreted by the industry and the FDA to apply only to data collected in clinical studies.

There may be reason to question Lilly's actions in regard to the reporting of foreign data, whether the regulations required it or not. But if the subcommittee's hearings revealed anything at all, it was that the agency's rules did not require full foreign data disclosure. If the subcommittee believes the FDA's pre-existing regulations were so clear and unambiguous, why does it also recommend that the FDA establish procedures for obtaining information concerning the safety and effectiveness of drugs under investigation from foreign countries in which the drugs have already been approved?

In point of fact, the FDA is to be commended for taking positive action in the matter of foreign data since the Oraflex issue arose. Proposed revisions of the NDA regulations, issued on October 19, 1982, would require "safety updates" for pending NDAs and proposed amendments to the IND regulations on June 9, 1983, would require reports of reactions associated with foreign commercial marketing.

It is not the role of the subcommittee to substitute its judgment for the FDA as to whether or not Oraflex should have been approved for marketing in the first place or if it should remain on the market. However, the subcommittee's report has added to the public record a generally reasonable discussion of some of the deficiencies of the drug approval process. It is apparent that the FDA has reconsidered its past practices, and has begun to clarify its reporting guidelines.

RAYMOND J. MCGRATH.

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Exhibit B

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Union Calendar No. 125

100th Congress, 1st Session - - - - - - - - - - House Report 100-206

FDA'S REGULATION OF THE NEW DRUG MERITAL

FIFTEENTH REPORT

BY THE

COMMITTEE ON GOVERNMENT OPERATIONS

JULY 8, 1987.—Committed to the Committee of the Whole House on the State of the Union and ordered to be printed

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U.S. GOVERNMENT PRINTING OFFICE

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LETTER OF SUBMITTAL

HOUSE OF REPRESENTATIVES,
Washington, DC, July 8, 1987

Hon. JIM WRIGHT,
Speaker of the House of Representatives,
Washington, DC.

DEAR MR. SPEAKER: By direction of the Committee on Gove
ment Operations, I submit herewith the committee's fifteer
report to the 100th Congress. The committee's report is based o
study made by its Human Resources and Intergovernmental R
tions Subcommittee.

JACK BROOKS, *Chairma*

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Union Calendar No. 1

100TH CONGRESS *1st Session* | HOUSE OF REPRESENTATIVES | REPORT 100-206

FDA'S REGULATION OF THE NEW DRUG MERITAL

JULY 8, 1987.—Committed to the Committee of the Whole House on the State of Union and ordered to be printed

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Mr. BROOKS, from the Committee on Government Operations, submitted the following

FIFTEENTH REPORT

BASED ON A STUDY BY THE HUMAN RESOURCES AND INTERGOVERNMENTAL RELATIONS SUBCOMMITTEE

On June 16, 1987, the Committee on Government Operations proved and adopted a report entitled "FDA's Regulation of New Drug Merital." The chairman was directed to transmit a c to the Speaker of the House.

I. INTRODUCTION

Under the rules of the House of Representatives, the Commit on Government Operations has responsibility for studying the o ation of Government activities at all levels. The committee has signed this responsibility as it relates to the Department of He and Human Services (HHS) to the Human Resources and Inter ernmental Relations Subcommittee.

The manner in which the Food and Drug Administration (F regulates the use and reviews the safety and efficacy of new dr has long been a major priority of the subcommittee. In the th years since the subcommittee last held hearings on FDA's poli and procedures for approving new drugs, there had been sev developments affecting the new drug review process. On Febru 22, 1985, FDA issued new regulations designed to speed the app al of new drugs.[1] In July 1985, FDA initiated a new managem Action Plan with the stated goal of expediting new drug approv At the same time, in recent years FDA has approved record n

[1] See 50 Fed. Reg. 7493.

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bers of new drugs, culminating in the approval of 30 new chemical entities in 1985.

In view of these developments, the subcommittee reexamined FDA's policies and procedures in this area. This reexamination initially focused on FDA's regulation of the new drug Merital (generic name nomifensine maleate), an anti-depressant manufactured by Hoechst-Roussel Pharmaceuticals, Inc., a subsidiary of Hoechst AG in Frankfurt, West Germany.[2] Merital was approved for marketing on December 31, 1984, six years after its new drug application (NDA) was submitted to FDA. On January 21, 1986, the sponsor announced that it was withdrawing the drug from the market because of a large number of hypersensitivity or allergic reactions associated with its use.

The subcommittee's investigation included a public hearing on May 22, 1986.[3] Witnesses included a noted medical expert in drug-induced allergic reactions and the Director and other representatives from the Office of Drug Research and Review, FDA's Center for Drugs and Biologics.

The subcommittee's investigation included careful examination of the relevant medical literature and of FDA documents, including correspondence, internal memoranda and information contained in the Merital NDA and investigational new drug (IND) files. In addition, the subcommittee obtained information on Merital from both public and private sources outside the United States. The comprehensive nature of this documentation enabled the subcommittee to evaluate the adequacy of FDA's policies and procedures for ensuring the safety and effectiveness of new drugs in general and Merital in particular.

II. Background

In October 1976, Hoechst AG began marketing Merital in West Germany. The following year, the drug was introduced in several other countries, including France, Great Britain, Ireland, Italy, Portugal, South Africa, and Switzerland.[4] The drug was being marketed in 31 nations[5] by the time Hoechst submitted its NDA for Merital on December 26, 1978.[6]

On February 27, 1979, FDA advised Hoechst that it was considering the possibility of not filing the Merital NDA because of major organizational deficiencies in the application.[7]

On March 13, 1979, Hoechst submitted four reports to FDA of immune hemolytic anemia, the destruction of red blood cells, associated with use of Merital in Europe. Three of these cases were known to Hoechst officials in Europe prior to the submission of the

[2] Hoechst-Roussel Pharmaceuticals, Inc., is also a subsidiary of Roussel Uclaf of France.

[3] Hearing before a Subcommittee of the Committee on Government Operations, House of Representatives, "Oversight of the New Drug Review Process and FDA's Regulation of Merital," May 22, 1986, hereafter referred to as Hearing.

[4] See Table S-1, "List of Countries Where Nomifensine is Sold," in Hoechst's May 7, 1984, submission to FDA, which is in subcommittee files.

[5] Ibid.

[6] Hoechst was originally granted an investigational new drug (IND) exemption for Merital in 1972.

[7] The memorandum of FDA's February 27, 1979, meeting with the sponsor is in subcommittee files.

Merital NDA. The reports were of sufficient concern that Hoechst was:

> . . . notifying all [U.S.] investigators currently treating patients of the European reports. All existing protocols will be amended to require a direct and indirect Coombs Test [a test for hemolytic anemia] for newly enrolled patients at baseline and termination.[8]

Hoechst AG had advised U.S. Hoechst of three of these four cases approximately two months earlier, when it suggested that they be reported to FDA since the agency was likely to learn of them anyway.[9]

After reviewing eleven protocols submitted by the sponsor, FDA's statistician wrote on July 16, 1979, that the sponsor had not presented "substantial evidence of the superiority of Merital as compared to placebo" in the treatment of the symptoms of depression.[10] On September 14, 1979, FDA's clinical reviewer similarly concluded that the sponsor had not submitted two "adequate and well-controlled trials which demonstrate substantial evidence of efficacy, the criterion for approval."[11]

Despite these conclusions, and serious deficiencies in the organization of the original Merital NDA submission, FDA brought Merital before its Psychopharmacologic Drugs Advisory Committee which on October 15, 1979, voted that it was "not able to identify sufficient studies supporting [the drug's] safety and efficacy."[12]

On December 28, 1979, FDA advised the sponsor that Merita was not approvable, largely because "the NDA does not contai 'substantial evidence [of efficacy] consisting of adequate and well controlled investigations,' a criterion for approval."[13] Thirtee months later, on January 28, 1981, FDA informed the sponsor tha the NDA remained not approvable because of problems in assess ing the evidence submitted in support of the drug's efficacy.[14]

Merital was again brought before the Psychopharmacologi Drugs Advisory Committee on December 3, 1981, which reviewe the efficacy evidence submitted for the drug and decided that th data were sufficient to support safety and efficacy.[15]

[8] Hoechst's March 13, 1979, submission is in subcommittee files.

[9] On January 10, 1979, an official in Hoechst's international headquarters in Frankfurt, We Germany, sent a "personal" and "confidential" letter to the residence of Dr. A. John Nelson U.S. Hoechst, advising of three reports of Merital-associated hemolytic anemia, one in Fran and two in the United Kingdom.

The author of the letter which is in subcommittee files, stated that he was "pretty sure th these cases will be published in a widely distributed Journal whilst our NDA is still in the l days processing." Consequently, he believed that "it is better to notify the FDA now, ratl than being asked later by them 'Why did not you inform us earlier?'"

Dr. Nelson received this letter on January 17, 1979. On January 18, 1979, he wrote Dr. Pola Hoechst AG, officially requesting materials concerning these three cases. This letter is in s committee files.

[10] Lucille P. Pogue's July 16, 1979, review is in subcommittee files.

[11] In subcommittee files.

[12] Four members voted in favor of this motion, while three abstained. See page 229 of verbatim transcript of this meeting, which is in subcommittee files.

[13] Hearing, page 371.

[14] In subcommittee files.

[15] The verbatim transcript of the advisory committee meeting is in subcommittee files. At meeting, the Psychopharmacologic Drugs Advisory Committee voted to recommend approva Merital partly on the basis of a pooling of several studies purporting to show efficacy, notw standing that FDA's biostatisticians had objected to the method by which these studies had b

Contin

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Dr. Robert Temple, Director, FDA's Office of Drug Research and Review, testified before the subcommittee that concerns about the evidence offered in support of Merital's "effectiveness remained the central focus of review and discussion for about the first four years of review" [16] of the Merital NDA.

However, after reviewing important safety information received over the previous 1½ years, most notably a July 22, 1981, Hoechst submission to the Merital IND concerning liver abnormalities associated with worldwide use of the drug that included four fatalities,[17] Dr. J. Hillary Lee, FDA's clinical reviewer for Merital, wrote in a February 23, 1982, memorandum:

> It is my impression that there are a number of serious adverse effects with this drug and I feel that perhaps the benefit risk ratio of nomifensine should be reconsidered based on these new data. I should say that we have been aware of the hemolytic and hepatic effects of this drug although perhaps the new reports suggest the effects are of a more serious degree than we previously thought.[18]

Two weeks later, at a March 8, 1982, internal meeting, Dr. Paul Leber, Director, FDA's Division of Neuropharmacological Drug Products, concurred with Dr. Lee that:

> . . . recently obtained data from Europe suggests a closer consideration of the drug's safety profile is needed. Rather than merely a question of efficacy, the drug's approvability may rest on a possible weak benefit/high risk ratio.[19]

Nonetheless, questions of the drug's efficacy continued to dominate FDA's review of the drug. Plagued by continuing doubts about the adequacy of the efficacy data submitted for Merital, FDA officials met with Hoechst on January 12, 1983, and suggested that the firm either "do additional studies" or that the "matter again go before an Advisory Committee." [20]

On February 25, 1983, FDA's Psychopharmacologic Drugs Advisory Committee met again and voted to reaffirm its previous determination that Merital had been shown to be a safe and effective antidepressant. The advisory committee, however, was not apprised of FDA's concerns that a "number of serious adverse effects" recently reported for Merital suggested that the "drug's approvability may rest on a possible weak benefit/high risk ratio."

FDA met again with the sponsor on May 23, 1983,[21] and Dr. Temple reminded the firm that the Merital NDA had been rather difficult because the drug's "effectiveness . . . had been a matter of some debate." [22]

Finally, however, on April 10, 1984, FDA notified Hoechst that Merital was approvable.[23] A month later, Hoechst submitted to FDA an international safety update concerning Merital.[24] During his review of this safety update, Dr. Thomas Hayes, the supervisory medical officer for Merital, apparently realized for the first time that some Merital-associated fevers reached temperatures as high as 40°C (104°F) or above. Based on this and what was already known about the toxicity of the drug, he recommended on July 2, 1984, that FDA rescind its determination that Merital was approvable:

> In view of the reactions reported in this submission, it appears necessary to reopen the question of the approvability of NOM [nomifensine] for depression. It should be recalled that at the time of initial submission, the NDA was judged to have failed to present sufficient evidence of efficacy to merit approval. It was later agreed after extended discussions that additional analyses provided a modicum of evidence of effectiveness applicable to the population for which it was intended, and there did not appear to be any prohibitive safety risks . . . Do these reports tip the balance away from approval? Certainly . . . The new disclosure of the problem of high fevers casts this in a different light, as far as I am concerned, and makes me feel that the risks outweigh the benefits for this drug. A careful appraisal of the data fails to disclose any benefit or contribution that the drug might offer to any identified or selected patient group which would justify exposing them to a treatment that causes adverse effects such as hemolytic anemia or high fever when the others don't. . . . I doubt that there is sufficient evidence of safety and efficacy to justify a recommendation of approval.[25]

Two weeks later, however, Dr. Hayes' superior, Dr. Leber, wrote that Merital-induced hyperpyrexia, or extremely elevated fever, should not prevent the drug's approval. Instead, Dr. Leber recommended, Merital should be approved on the condition that it be limited to *second-line use*. It should be marketed with labeling that "restricts its use to patients who have failed to respond to standard treatments." [26]

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pooled. Following the meeting, FDA's Division of Biometrics maintained that the advisory committee did not consider major statistical problems with the data presented it. See Hearing, page 11.

[16] Hearing, page 10.

[17] This submission is in subcommitee files.

[18] In subcommittee files.

[19] In subcommittee files.

[20] The memorandum of this meeting appears at Hearing, page 421.

[21] In requesting such a meeting, Hubert E. Huckel, Chairman of the Board of Hoechst's U.S. affiliate, wrote FDA on March 11, 1983:

> Another aspect important to our relatively small U.S. company is that our Board of Directors has refused to allow an increase in sales force personnel and the number of scientists working in our research laboratories until new product approvals are received. With receipt of the NDA approvals we would create immediately 50 new positions in the sales force, would add about 20 employees in production, and would also bring an expansion of our research department. Surely at a time when unemployment is so high, and national attention is directed towards improving the situation, even these small additions of jobs for the workforce should not be overlooked.

This letter is in subcommittee files.

[22] This memorandum is in subcommittee files.

[23] Dr. Temple's April 10, 1984, approvable letter is in subcommittee files.

[24] This May 7, 1984, update is in subcommittee files.

[25] Hearing, pages 187-8.

[26] Dr. Leber's July 17, 1984, memorandum appears in Hearing, pages 385-9.

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Dr. Temple concurred with Dr. Leber's *second-line use* recommendation,[27] and on August 1, 1984, FDA sent Hoechst a second approvable letter for Merital, this time restricting the drug to *second-line use.* The letter concluded:

> Your safety update has provided new information about a previously unappreciated risk of nomifensine, hyperpyrexia. In our judgment, hyperpyrexia—although reported infrequently to date—has more serious implications that the low grade temperature elevations of which we were aware. . . . This newly discovered serious reaction, coupled with the known unusual profile of risks of nomifensine requiring careful monitoring for hemolytic anemia and liver abnormalities, causes us not to consider nomifensine a first choice drug in depression. . . . [A]t present we consider nomifensine to be approvable only for a population of depressed patients unresponsive to, or intolerant of, other agents.[28]

A Hoechst official swiftly moved to overturn FDA's decision on *second-line use,* in a conversation recorded in a memorandum by Dr. Thomas Hayes:

> Mr. Bucceri [Vice-President Regulatory Affairs of Hoechst's U.S. affiliate] said they were surprised at the stringency of the labeling requirements. . . . He wondered if we might agree not to require the paragraph on [second-line use] if they presented new information. I said . . . I did not think we would be receptive to approving the drug without the paragraph in question.[29]

This was followed by an October 31, 1984, letter from Hoechst to Dr. Temple complaining that the labeling of Merital as a second-line anti-depressant "virtually precludes the marketing of this drug." [30]

On December 21, 1984, FDA officials were reportedly "able to resolve" all "outstanding issues" regarding final approval of the Merital NDA during a teleconference with the sponsor,[31] including the approval of the Merital NDA without the second-line limitation.[32] Accordingly, on the final day of 1984, FDA approved Merital for marketing *without the second-line use restriction.*[33]

[27] Dr. Temple's July 27, 1984, memorandum appears in Hearing, pages 427-8. Dr. Temple acknowledged, however, that "We . . . do not have a precisely defined subset of patients in whom [Merital] is known to be a useful second line agent" but only "a strong expectation, given clinical variability, that it will sometimes prove useful in people who failed on other agents."

[28] In subcommittee files.

[29] Dr. Hayes' memorandum of this August 7, 1984, telephone conversation is in subcommittee files.

[30] This letter from Victor J. Bauer, Executive Vice President, and A. John Nelson, Senior Vice President and Medical Director, both of Hoechst's U.S. affiliate, appears in Hearing, pages 350-2.

[31] The sponsor, according to a December 26, 1984, letter to FDA, was "able to resolve" all "outstanding issues" with FDA regarding final approval of the Merital NDA during this teleconference. No FDA memorandum was written of this important contact. See FDA's November 5, 1986, letter to the subcommittee, Hearing, page 487.

[32] One week after this teleconference, Dr. Leber recommended that Merital be approved without this limitation. His December 28, 1984, memorandum appears at Hearing, pages 339-349.

[33] Hearing, page 12.

Although the sponsor had complained about FDA's delays in ap proving the drug, it did not launch its marketing campaign fo Merital until late July 1985. In the meantime, the safety of Merita became the subject of considerable concern in Europe.

In February 1985, a German medical publication published warning on Merital which stated:

> The antidepressant nomifensine can *induce an immune-allergic reaction,* which usually manifests itself within three weeks after the beginning of treatment in fever, serum sickness-like complaints with muscle aches, joint pain and flu symptoms and can proceed with blood damage (thrombocytopenia) and pathological liver function including granulomatous hepatitis. A north German group of physicians now also describe symptoms of lung involvement with the clinical picture of bronchopneumonia. . . .[34] [Emphasis supplied.]

In addition, on February 1, 1985, the Adverse Drug Reactic Committee of the Drug Commission of the German Medical Profe sion met and decided to issue a warning about possible "allergi reactions involving several organ systems that had been observ among Merital patients.[35] It appeared in the March 27, 1985, *Dei sches Arzteblatt.* [36]

In early 1985, Hoechst also received several reports of Merit associated deaths involving immune hemolytic anemia. These cluded a report of a 37-year-old British woman who had restart Merital, having previously discontinued it after 6 or 7 days becau of dizzy spells. Within one hour of restarting, she collapsed a upon admission to the hospital, was diagnosed with severe int vascular hemolysis. Acute renal failure also occurred, and dialy was considered. Shock lung syndrome ensued and she died on F ruary 10, 1985. A report of this death, including a manuscript s by two consulting hematologists to the *British Medical Jour* concerning the case,[37] was submitted to FDA on April 15, 198

On May 9, 1985, Dr. Hayes, the supervisory medical officer Merital, recommended that "warning statements" in that label "be revised and strengthened to convey the seriousness of hemo ic reactions to this drug." [39]

On May 21, 1985, Hoechst submitted a report to FDA concern two additional Merital-associated hemolytic anemia deaths fr

[34] Translated from the German. See "The Alveolitis-Influenza-Like Syndrome with Nom sine," appearing in the February 1985 issue of the Arznei-telegramm, which is in subcomm files.

[35] The memorandum of this meeting is in subcommittee files.

[36] This warning is in subcommittee files.

[37] The *British Medical Journal* published the case on August 3, 1985. See Sokol, H Booker, Stamples, and Taylor, "Fatal immune haemolysis associated with nomifensine," *B Medical Journal,* vol. 291, pages 311-2.

[38] The records referred to in this case were all included in the April 15, 1985, submissi FDA, which is also in subcommittee files. The sponsor submitted a follow-up report to FI the case on September 11, 1985, which is also in subcommittee files.

On March 19, 1985, Dr. Suzanne M. Streichenwein of Hoechst AG, accompanied by tw cials of Hoechst UK, visited the hospital to obtain more information on the case. Obvi Hoechst officials were notified of the case some time before this, although none of the re submitted to FDA by the sponsor indicates this notification date. On March 28, 1985, H AG officials forwarded records on the case to Dr. A. John Nelson of Hoechst's U.S. affiliate

[39] His May 9, 1985, memorandum is in subcommittee files.

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the United Kingdom, involving a 43-year-old and 27-year-old woman.[40] Hoechst did not report, at this time, at least one additional Merital-associated death possibly involving hemolytic anemia that had been brought to its attention. This case, involving a German woman, was received by Hoechst AG on April 23, 1985,[41] but it was not reported to FDA until September 16, 1985.[42] Hoechst's U.S. affiliate learned of the case by June 10, 1985.[43]

In anticipation of a June 25-26, 1985, Tripartite Meeting with the British and Canadians, Dr. Robert Temple, noting that "the British expressed concern regarding hematological toxicity of nomifensine and wanted to know about any knowledge or experience we might have had," requested information on this subject.[44]

Responding to this request, Dr. Thomas Hayes wrote on June 11, 1985, that FDA had received one report of a fatal hemolytic anemia case associated with use of the drug outside the United States,[45] even though by that time Hoechst had in fact reported three such cases to FDA.

Two days later, FDA asked Hoechst to revise the warnings section to "convey the seriousness of hemolytic reactions to this drug."[46] On June 25, 1985, Hoechst strengthened the hemolytic anemia warning, although not completely to FDA's satisfaction.[47]

In June 1985, Hoechst received a report of an August 8, 1983, death of a 62-year-old Canadian man who also appeared to have experienced a hypersensitivity or allergic reaction to Merital.[48] A pathologist diagnosed the patient as having suffered "drug induced hypersensitivity vasculitis [inflammation of the peripheral blood vessels] and myocarditis [inflammation of the muscular walls of the

[40] Hoechst's May 21, 1985, submission is in subcommittee files. A follow-up report on these cases was submitted to FDA on September 11, 1985. In subcommittee files.

[41] According to a September 10, 1985, letter to Hoechst Canada, which is in subcommittee files, Hoechst AG officials stated: "[W]e received the first notification ever about this case from the patient's physician on April 23, 1985." Merital-specific antibodies had been detected in the serum of a hemolytic anemia patient who died several years earlier. The serum of a German woman was found in 1981 to exhibit "warm auto-immune haemolysis." While testing a new antibody detection method in 1985, a German researcher reportedly found Merital-specific antibodies in her serum. Hoechst AG made an on-site visit in connection with this case on May 6, 1985.

[42] This report is in subcommittee files.

[43] See the inspectional observations issued by FDA field investigators to Hoechst's U.S. affiliate (FDA form 483) in March 1987, in subcommittee files.

[44] His memorandum is in subcommittee files.

[45] His memorandum is in subcommittee files.

[46] FDA's June 13, 1985, letter is in subcommittee files.

[47] In a June 25, 1985, letter, Hoechst submitted to FDA revised labeling that was to be effective immediately in accordance with 21 CFR § 314.70(c)(2). The new hemolytic warning read as follows: "Rare occurrences of severe hemolytic anemia which could lead to potentially fatal complications have been reported after treatment with Merital (nomifensine maleate) from two weeks up to fourteen months." In subcommittee files.

However, FDA's clinical reviewer, Dr. J. Hillary Lee, recommended in a July 3, 1985, memorandum that the labeling specifically state that:

> Cases of severe, life threatening, hemolytic anemia have been reported following treatment with Merital. As of mid-1985, three deaths from this cause have been reported from world-wide sources.

In subcommittee files.

[48] The patient's psychiatrist completed a Hoechst adverse reaction report on the case on June 5, 1985. On June 17, 1985, he also advised an official of Hoechst Canada of the case. In a June 25, 1985, letter to him, Dr. R. LaCombe, Medical Director, Hoechst Canada, wrote: "Also, from a telephone conversation you had with Dr. R. Laliberte [of Hoechst Canada] on June 17, 1985, we note that you have agreed to provide us with information regarding the other case—a 62 year old male patient."

heart]." The sponsor did not submit the case to FDA as a "15-day alert" report, however, until September 16, 1985.[49]

In July 1985, the United Kingdom's Committee on Safety of Medicines reported that it had received 33 reports of Merital-associated hemolytic anemia, including 3 deaths, and noted that the drug "has also been associated with an influenza-like syndrome characterized by malaise, pyrexia, myalgia, and arthralgia or arthritis."[50]

On July 27, 1985, *The Lancet* reported two fatal cases of necrotising vasculitis associated with use of nomifensine in Germany. Noting that the drug "can cause immune-allergic adverse reactions," the report concluded that "clinicians need to realize that nomifensine may cause these symptoms, since otherwise they may be misinterpreted as signs of an acute bacterial or viral disease (septic shock)."[51] Although one of the authors advised the subcommittee staff that he reported these cases to Hoechst shortly before they were published,[52] the company did not report this article to FDA as a "15-day alert" report until September 5, 1985.

By mid-August 1985, Hoechst learned of a July 14, 1985, death possibly resulting from an allergic reaction to Merital, this one involving a 79-year-old Dutch woman who experienced hepatitis, a veolitis, and a secondary "hepatorenal syndrome.[53] No mention of the case was made to FDA until October 31, 1985.[54] Many details regarding the case were not forwarded to the agency until January 3, 1986.[55]

By August 1985, the German medical publication which, in February 1985, had warned physicians about severe immune-toxic reactions to Merital, was recommending that physicians use alternative drugs since, in its judgment, Merital's risks outweighed its benefits.[56]

At the direction of the German Federal Health Office, Hoechst sent a warning letter on September 24, 1985, to all doctors and pharmacists in Germany, which reviewed several reports of "hypersensitivity" reactions associated with use of the drug, including three fatal cases of immune hemolytic anemia, two fatal cases of immune vasculitis, one fatal case of acute liver dystrophy,[57] and one case of lupus erythematosis.[58]

[49] Report is in subcommittee files. Hoechst also submitted a February 7, 1985, manuscript had received on the case that the patient's psychiatrist had submitted for publication.

[50] See the July 1985 issue of *Current Problems*, which is in subcommittee files.

[51] See Schoenhoefer, Goeticke, "Fatal Necrotising Vasculitis Associated with Nomifensine," July 27, 1985, *The Lancet*, page 221.

[52] The memorandum of a May 7, 1986, conversation is in subcommittee files.

[53] See a memorandum of an August 16, 1986, telephone conversation with Dr. Sumaj Hoechst Holland, by Dr. Suzanne M. Streichenwein of Hoechst AG. On August 29, 1985, Streichenwein was informed that "three physicians intend to publish this case." In view of w Hoechst AG regarded as "the importance of this case for pharmaceutical policy," (see Dr. St chenwein's memorandum of her August 16, 1985, conversation with Dr. Sumajow) Drs. St chenwein and Mohr of Hoechst AG visited Holland to discuss the case on September 19, 1

[54] Hoechst's October 31, 1985, report of this case is in subcommittee files.

[55] Most of the details that appear here concerning the case are from the sponsor's Januar 1986, submission, in subcommittee files.

[56] See article entitled, "On the Immune Toxicity of the Antidepressant Nomifensine," that peared in the August 1985 issue of the Arznei-telegramm, in subcommittee files.

[57] This obviously referred to the Dutch case, which also involved alveolitis and secon renal failure. This case was not even reported to FDA until October 31, 1985, approximately weeks following the issuance of this warning letter.

[58] The letter is in subcommittee files.

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Hoechst sent a similar letter to physicians in the United Kingdom on September 30, 1985.[59] This letter advised that, "in the light of recent reports of adverse reactions in association with nomifensine (Merital)," revised labeling was under discussion with U.K. regulatory authorities in which "more emphasis will be given to hypersensitivity reactions."[60] At that time, Hoechst also suspended all written and oral promotion of the drug to doctors and pharmacists.[61]

On October 31, 1985, Hoechst reported eight deaths to FDA, including the Dutch case involving alveolitis, acute liver dystrophy, and secondary renal failure; a 1984 British case involving cardiac arrthymia and shock in the face of anemia; and a 1982 French case involving "allergic" exfoliative dermatitis and pneumonitis.[62]

On November 1, 1985, Hoechst submitted a report of large numbers of adverse reactions—including hemolytic anemia, liver injury, alveolitis/lung disorder/dyspnea/pneumonitis, and fever—associated with worldwide use of the drug that reportedly came to the U.S. affiliate's attention since the international safety update it submitted to FDA on May 7, 1984.[63] On November 8, 1985, the sponsor met with FDA to discuss "immunologic ADRs [adverse drug reactions]."[64] At the meeting, the firm agreed to Dr. Leber's recommendation that it restructure the Merital labeling to emphasize the immunological basis that FDA thought might underlie several of the adverse effects associated with use of the drug.[65]

Thus, the labeling that went into U.S. distribution channels in December 1985 warned for the first time of a presumed immunological basis for many of the reactions, including some that had proven life-threatening, that had been reported for Merital.

A December 7, 1985, update from the United Kingdom's Committee on Safety of Medicines that appeared in the *British Medical Journal* concluded that Merital carried higher risks than all other new antidepressants being marketed.[66] The drug was associated with substantially more reports of hemolytic [67] and hepatic [68] reactions than other second generation antidepressants. The drug had also been associated with more reports of death than any antidepressant—old or new—then on the British market.[69]

On December 9, 1985, Hoechst AG received yet another report of a Merital-associated hemolytic anemia fatality, this one involving a 66-year-old German woman that had occurred on June 17, 1985. FDA did not receive a report of this case, however, until February 5, 1986, almost two months later.[70]

[59] In subcommittee files. The letter reviewed the same cases summarized in the September 24, 1985, German warning letter.

[60] Ibid.

[61] See *The Lancet*, February 1, 1986, page 281.

[62] See the subcommittee's June 13, 1986, letter to FDA, Hearing, pages 433 and 436-7.

[63] Hearing, pages 190-208.

[64] See the memorandum of this meeting by Tony DeCicco, consumer safety officer, Hearing, page 147.

[65] See the November 13, 1985, letter from Mr. Dennis Bucceri, of Hoechst's U.S. affiliate, to Dr. Leber, in subcommittee files, Hearing, page 446.

[66] See "CSM Update," Vol. 291, page 1638.

[67] Merital had attracted 28 hemolytic anemia reports per million prescriptions, compared to 1 for maprotiline and less than 1 for mianserin.

[68] Merital attracted 53 reports of hepatic injury per million prescriptions, compared to 9 such reports for mianserin and 2 for maprotiline.

[69] Seven fatal adverse reactions had been reported to the CSM per million prescriptions.

[70] Hoechst's February 5, 1986, submission is in subcommittee files.

On December 16, 1985, the British *Drug and Therapeutics Bulletin* mentioned another drug-associated hemolytic anemia fatality that had been reported to the British authorities but not to Hoechst.[71] The article concluded that "in most patients, the risks, and the vigilance required to minimise them, overshadow the therapeutic advantages previously claimed for it over the tricyclic antidepressives." It also criticized Hoechst's September 30, 1985, U.K. "Dear Doctor" letter, not only for its failure to "accept in any of the six cases [of hypersensitivity reactions it mentioned] the causal relationship with nomifensine," but also its promotional tone, which was "likely to undermine the authority of the CSM's warning about the dangers of using nomifensine" and "which may be thought to amount to contempt of the CSM [the United Kingdom's Committee on Safety of Medicines]."[72]

Two days following publication of this article, Hoechst U.K. distributed to U.K. physicians another "Dear Doctor" letter which called attention to Merital-associated "hypersensitivity reactions" and expressed particular concern about "reports of hepatic reactions, an influenza-like syndrome and blood disorders, notably haemolytic anaemia."[73] Accompanying the letter was revised U.K. labeling which stated that "Merital should be discontinued immediately after the onset of the first signs of a [hypersensitivity] reaction and not used again under any circumstances."[74]

On January 8, 1986, the British trade publication, *SCRIP*, "suggested that the CSM might be on the verge of taking some sort of action against nomifensine."[75] At the request of FDA's Dr. Temple, a copy of this article was provided to Dr. Leber on January 13, 1986,[76] and on that same day, Dr. Leber contacted Hoechst to request a copy of the recent U.K. "Dear Doctor" letter, as well as all information about the drug currently being published in the U.K. by regulatory authorities. He also asked that they keep him fully informed of any pending action by British regulators.[77]

Dr. Leber also contacted British authorities directly and learned that they were concerned about Merital's risk-to-benefit ratio, planned to discuss the matter before a subcommittee of the CSM, and that reports of Merital-associated hemolytic anemia had increased dramatically, without clear explanation, during 1984 and 1985.[78]

On January 16, 1986, Dr. Michael Murphy, Director of Psychopharmacology of Hoechst U.S., called Dr. Leber to inform him that the South Africans were modifying Merital's labeling to advise that it be used cautiously, and then only for seriously ill patients.[79] D

[71] In a January 21, 1986, letter to FDA, Dr. Michael F. Murphy, Director of Psychopharmacology of Hoechst's U.S. affiliate, wrote: "A death noted in the *Drug and Therapeutics Bulletin* was reported directly to CSM. Hoechst U.K. has no further information on this case." In subcommittee files.

[72] See "Trouble with Nomifensine," Vol. 23, No. 254, pages 98-100.

[73] In subcommittee files.

[74] In subcommittee files.

[75] See a January 27, 1986, memorandum, from Dr. Paul Leber, Director, FDA's Division Neuropharmacological Drug Products, which is in subcommittee files.

[76] Ibid.

[77] Ibid.

[78] Ibid.

[79] Ibid. Dr. Murphy also implied that the CSM would meet to consider a similar insert revision for the U.K. labeling.

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Leber could not have known at this time that, on November 6, 1985, Hoechst AG had received a report of the October 30, 1985, death of a 23-year-old South African woman involving hemolytic anemia in conjunction with jaundice and acute kidney failure.[80] Hoechst's U.S. affiliate was notified of the case by December 23, 1985.[81] That death was not reported to FDA until February 5, 1986, four months after Hoechst AG was notified of it and almost three weeks after Dr. Leber's conversation with Dr. Murphy of Hoechst.[82]

A January 16, 1986, quarterly report to FDA covering U.S. marketing of the drug during the final quarter of 1985 included 547 reports of adverse reactions, 49 of which involved reactions Hoechst classified as serious, and 7 of which involved hemolytic anemia reactions.[83] In addition, the submission reported the hemolytic anemia-related death of a 76-year-old woman who also had "preexisting severe liver disease" that was reported to the sponsor on December 2, 1985.[84]

On January 20, 1986, a Federal holiday, a Hoechst official called Dr. Leber at home to state that the company was withdrawing Merital from the market.[85] The following day, Dr. Leber called Hoechst and learned that a worldwide withdrawal was being announced.[86]

Hoechst stated in a draft withdrawal letter sent to FDA on January 21, 1986, that it was removing the drug from the market because of "an increase in the number of reports of serious hypersensitivity reactions, notably hemolytic anemia, occurring in nomifensine-treated patients in the United Kingdom." [87] In an accompanying letter, the firm advised FDA that it did "not consider a withdrawal to the patient level as necessary because current labeling adequately addressed these issues and the size of prescriptions is small and, thus, self-limiting." [88] On January 22, 1986, the firm further advised FDA that it would issue a press release on its withdrawal "[o]nly if the volume of questions becomes overwhelming . . ." [89]

Based on two submissions to FDA, one in January 1986 and one in April 1986, Hoechst listed at least 353 U.S. reactions that it classified as hypersensitivity reactions to Merital that were reported during the drug's brief and relatively limited marketing in the United States.[90] Additional such reactions occurring in the U.S. have been reported by the sponsor in subsequent submissions.

[80] The reaction onset date was October 18, 1985. From the information available in FDA's files, it cannot be ascertained when the death first came to the attention of Hoechst's South African affiliate. However, that affiliate's medical director visited and discussed this case on November 4 and 5, 1985, with the registrar of the Medicines Control Council, Pretoria.

[81] See the inspectional observations issued by FDA field investigators to Hoechst's U.S. affiliate (FDA Form 483) in March 1987, in subcommittee files.

[82] Hoechst's February 5, 1986, submission to FDA is in subcommittee files.

[83] In subcommittee files.

[84] Ibid. The sponsor was informed of the case in late October 1985, but did not receive a report of the patient's death until December 2, 1985.

[85] See Dr. Leber's January 27, 1986, memorandum, which is in subcommittee files.

[86] Ibid.

[87] In subcommittee files.

[88] In subcommittee files.

[89] Hoechst's January 22, 1986, letter is in subcommittee files.

[90] Hearing, page 20.

Deaths have continued to be reported following Merital's market withdrawal. For example, on October 21, 1986, Hoechst reported to FDA another Merital-associated fatality in the United States possibly involving hemolytic anemia.[91] On February 3, 1987, Hoechst reported the Merital-associated death of an Arkansas woman that also involved hemolytic anemia as well as jaundice and other disorders.[92] Another hemolytic anemia fatality on January 21, 1986, involving a 64-year-old female German Merital patient was reported to FDA on March 25, 1986,[93] as was a death from malignant neuroleptic hyperthermia syndrome involving a 60-year-old Irish woman.[94] On July 30, 1986, Hoechst reported additional deaths, including a French case of extrapyramidal syndrome [95] and a U.K. case of disseminated intravascular coagulation.[96] On August 19, 1986, Hoechst reported the death of a 36-year-old French woman associated with hemolytic anemia in combination with thrombocytopenia and disseminated intravascular coagulation.[97]

While FDA was advised that "Hoechst AG decided voluntarily to withdraw Merital from worldwide distribution," [98] the United Kingdom's Committee on Safety of Medicines, in an update published in the July 5, 1986, *British Medical Journal*, stated that reports received of Merital-associated adverse reactions "suggested hazard which was unacceptable when effective alternative remedies were available." [99]

On June 17, 1986, FDA removed Merital from the list of approved drugs because it had been withdrawn from the market for safety reasons.[100]

On January 9, 1987, one year after Merital was removed from the world market, Hoechst requested that FDA withdraw approval of the Merital NDA.[101]

[91] The report of this case is in subcommittee files. In a December 4, 1986, submission, however, Hoechst included a consultant's report that argued against "a nomifensine induced hemolytic anemia or any type of hemolytic anemia" as being responsible for the death of the 54-year-old patient. In subcommittee files.

[92] The February 3, 1987, report of this March 4, 1986, death is in subcommittee files. The patient had previously been diagnosed with Hodgkin's lymphoma. See the January 22, 1987, letter to the subcommittee from the lawyer for the patient's estate, in subcommittee files.

[93] The patient died 12 hours after being admitted to the hospital. The records on this case are in subcommittee files.

[94] On February 24, 1986, Hoechst Ireland Ltd related this death to Hoechst AG. Records on the case are in subcommittee files. In an October 29, 1984, submission, Hoechst listed "neuroleptic malignant syndrome" as one of many "signs commonly observed in extreme pyrexia [fever]." In subcommittee files.

[95] Records on this case are in subcommittee files. In an October 29, 1984, submission to FDA, Hoechst had listed "extrapyramidal symptoms" as among "signs commonly observed in extreme pyrexia [fever]" that "have not been reported" for Merital. In subcommittee files. However, in an April 24, 1986, quarterly report for Merital, the sponsor reported a French case of extrapyramidal syndrome known to it since 1982. In subcommittee files. A Merital associated case of acute extrapyramidal reaction to nomifensine in a 77-year-old woman was also reported in the November 10, 1984, *British Medical Journal*, see vol. 289, page 1272.

[96] Records on the death of this 37-year-old female are in subcommittee files.

[97] On February 28, 1986, reportedly some time after she discontinued use of Merital in December 1985, the patient developed acute hemolysis, thrombocytopenia, disseminated intravascular coagulation, hypertension, renal failure and pulmonary edema and subsequently died on March 3, 1986. Records on the case are in subcommittee files.

[98] See Hoechst's January 22, 1986, letter to FDA, in subcommittee files.

[99] "Withdrawal of nomifensine," July 5, 1986, *British Medical Journal*, Vol. 293, page 41.

[100] 51 Fed. Reg. 21981.

[101] Hoechst's January 9, 1987, letter to FDA is in subcommittee files.

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III. Summary of Findings and Conclusions

1. Prior to approving Merital, FDA overlooked evidence of the drug's allergy-inducing potential

Prior to its approval by FDA in 1984, Merital was associated with various combinations of signs and symptoms, including eosinophilia (an abnormally high count of a certain kind of white blood cells); fever; joint and muscle pain; skin rashes; abnormal liver functioning; hemolytic anemia (destruction of red blood cells), sometimes accompanied by kidney failure; thrombocytopenia (depressed blood platelet counts); and lung infiltrates.

Dr. N. Franklin Adkinson, Jr., an Associate Professor of Medicine with a joint appointment in the Subdepartment of Immunology of the Johns Hopkins University School of Medicine, testified before the subcommittee that such pre-approval reports suggested that Merital was associated with immunological or allergic side effects. His assessment was reiterated by a number of noted experts in drug-induced immune reactions consulted by the subcommittee. Shortly before the drug was approved, Merital's sponsor acknowledged that many signs and symptoms reported for the drug that occurred in various combinations suggested that Merital was associated with an immune syndrome or group of syndromes. Despite this, the labeling originally approved by FDA did not acknowledge a common immunological basis for many of the adverse reactions that had been reported for the drug and did not warn that serious reactions such as hemolytic anemia probably constituted part of a Merital-induced immune syndrome.

Dr. Robert Temple, Director, FDA's Office of Drug Research and Review, conceded that many of the signs and symptoms reported for the drug "can be and perhaps should earlier have been recognized as all related to immune complex formation." He maintained, however, that such recognition was not relevant to the agency's consideration of whether and how Merital could be safely used. What mattered to FDA, he testified, was the incidence and severity of Merital-associated adverse reactions—i.e, the actual damage to patients—not whether an immunological mechanism was responsible for them.

Since allergic drug reactions, by definition, are those that involve an immunological mechanism, the implication of Dr. Temple's testimony is that it was not important in evaluating Merital's safety to recognize that potentially serious Merital-associated side effects represented allergic reactions to the drug.

The central deficiency in FDA's pre-market regulation of Merital's safety was the agency's failure to recognize the drug's significant allergenic potential. A review of the extensive medical literature devoted to the clinical diagnosis and management of drug-induced allergic reactions contradicts FDA's position that recognition of Merital's capacity to cause immunologically mediated or allergic reactions was unimportant. Allergic drug reactions, unlike other toxic drug effects, can be precipitated by minute amounts of a drug, far below therapeutic doses. Thus the literature repeatedly states that allergenic drugs should be discontinued in patients

known to be sensitive to them, and especially where therapeutic a ternatives are available.

Allergic reactions generally occur upon re-exposure to a dru after a previous period of use and sensitization. Since depressed p tients are likely to use an anti-depressant episodically, any pote tially serious, dose-independent toxicity attendant upon re-exposu to an allergenic drug is germain to whether or how it can be safe used as an antidepressant.

Serious Merital-associated allergic reactions were often precede by more benign allergic responses occurring upon one or mo prior exposures. Assuming that Merital was approvable, awarene that benign allergic manifestations such as fever or flu-like sym toms could lead, upon continued exposure, to severe, even lif threatening allergic reactions such as hemolytic anemia was esse tial to early detection and clinical management of potentially se ous Merital-induced allergic disorders. Merital's labeling did n warn physicians to be alert to mild allergic reactions that their p tients might experience. It, thus, did not bear "adequate directio for use" and was misbranded within the meaning of the law.

FDA testified that the agency did not believe it important alert physicians to Merital's apparent immune or allergic toxici But once the agency concluded that many Merital-associated a verse effects might have a common immunological origin, t agency asked Hoechst to re-label the drug to warn about this as means of alerting physicians to the drug's allergic potential. So thereafter, Hoechst removed Merital from the market.

2. The detection of drug-specific antibodies in an extraordinarily high percentage of Merital patients further evidences the drug's allergenic potential

Antibodies are proteins produced by the body in response to foreign substance, such as a drug they can recognize. In some cas they react with that substance to induce an allergic reaction. Lab ratory investigations have confirmed that antibodies were respon ble for many of the allergic reactions reported for Merital.

A person developing antibodies against a drug and/or its meta lites (i.e., its breakdown products in the body) is said to exhibit immune response to it. Allergic drug reactions, by definition, a adverse effects that can be attributed directly to such a respon Thus, tests for immunological drug reactions are often directed detecting the presence of drug-specific antibodies in a patien blood.

Merital was reported to be highly immunogenic—that is, it v found to be associated with a high degree of drug-specific antib formation. A Swiss paper in December 1983 reported that Meri specific antibodies were detected in the blood of 51 of 51 patie who took the drug. Subsequent work by the authors revealed t approximately 88 percent of a total of 105 persons given Mer developed drug-specific antibodies. This degree of drug-specific a body formation was highly unusual, if not unique.

It was not until the subcommittee's May 22, 1986, hearing t FDA learned that Merital had been reported to be highly immu genic. Dr. Robert Temple testified that the antibody findings

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Merital would have been of little significance to FDA unless they could be correlated with clinically observable adverse reactions. However, such findings would have signaled the drug's potential to induce allergic reactions. Drugs that engender a drug-specific immune response (i.e., antibodies) are more likely to induce allergic reactions than drugs that do not stimulate the immune system. Had FDA been aware, prior to approving Merital, that the drug was exceptionally immunogenic, it might not have overlooked the abundant clinical evidence it received of Merital's capacity to induce a wide range of allergic reactions. Moreover, it was concern over reports of adverse reactions to Merital, most notably hemolytic anemia, that had earlier prompted Hoechst to embark on an extensive program throughout Europe to look for specific antibodies in the blood samples of Merital patients. Similarly, the authors of the December 1983 Swiss paper decided to do antibody studies on Merital blood samples because they believed the drug induced adverse reactions that appeared to be of immunological origin.

Prior to the approval of Merital, the sponsor failed to report to FDA several serious and sometimes fatal reactions to the drug of a possibly allergic nature. The significance of data on Merital's immunogenicity would have been enhanced had these reactions been reported.

3. FDA DID NOT ENSURE RECEIPT AND REVIEW OF IMPORTANT INFORMATION PERTINENT TO ITS ASSESSMENT OF THE SAFETY OF MERITAL

A. FDA's Regulation of Merital Did Not Include Review of Important Publications in the World Literature Relevant to the Drug's Safety

Numerous publications appeared in the world literature from 1979 through 1984 documenting the clinically diverse manifestations of Merital's apparent immune toxicity. FDA's regulation of the safety of Merital did not include consideration of these publications.

It is essential that FDA make every effort to obtain and review all publications in the world literature necessary for a responsible assessment of the safety and efficacy of a new chemical entity.

The titles and very frequently the abstracts of articles published in tens of thousands of publications in the world literature are entered into Medical Literature Analysis and Retrieval System (MEDLARS), which is maintained by the National Library of Medicine. The computer printouts generated from MEDLARS enable virtually the entire world literature concerning a new drug under review to be scanned in a very condensed form. The MEDLARS printout for "nomifensine" contained English titles and/or English abstracts for most of the publications, including foreign language publications, concerning Merital's potential to induce allergic reactions. Although FDA's library has computer access to this system, the agency does not require its reviewers to obtain and examine titles and, where available, English abstracts accessed from this system for relevant publications concerning new drugs under their review.

B. FDA Does Not Require the Submission of Labeling, "Dear Doctor" Letters, and Other Important Regulatory Information Related to the Foreign Marketing of New Drugs Under Review in the United States

Well before FDA approved Merital, the drug's German labeling warned physicians about several "immunologically caused hypersensitivity reactions" associated with the drug's use, the occurrence of any one of which necessitated immediate discontinuation of the drug. No such warning appeared in the labeling originally approved by FDA.

FDA did not receive a copy of this labeling. The agency does not require sponsors to submit to it all labeling, or changes in labeling, for a new drug approved in other nations that is either under investigation or has been approved for marketing in the United States. Such a requirement could provide valuable additional information on the manner in which foreign regulatory authorities as well as sponsors view a new drug under FDA review.

In February 1985, several months before Merital's market launch in the United States, Hoechst sent a "Dear Doctor" letter to German physicians emphasizing information concerning the "influenza-like syndrome" and other hypersensitivity reactions associated with Merital's use. FDA did not receive a copy of this letter. Nor did the agency receive "Dear Doctor" letters sent to German and U.K. physicians in September 1985 warning of several serious and sometimes fatal reports received of Merital-associated "hypersensitivity" reactions.

FDA does not require sponsors to submit "Dear Doctor" letters distributed to practitioners in other nations concerning new drugs under review in the United States. Had it done so, it might have learned that the sponsor was emphasizing to foreign physicians aspects of Merital's toxicity that were not featured in the package inserts then available to American physicians.

FDA did not learn until January 1986 that as of September 1985 Hoechst had stopped promoting Merital in the United Kingdom. In addition, it was not aware that the U.K.'s Committee on Safety of Medicines (CSM) was raising questions about the continued approvability of the drug. Were FDA to require sponsors to inform it of important regulatory developments concerning new drugs marketed outside the United States that are under investigation or have been approved for marketing here, it could keep abreast of events that might provide it with valuable additional insights into these drugs.

A May 1981 evaluation from Australia's Department of Health noted that Merital may induce allergic reactions consisting of one or more signs and symptoms that may comprise part of a syndrome. Hoechst obtained this evaluation in August 1983, but never forwarded it to FDA. Similarly, FDA was not informed that Hoechst withdrew its marketing application for Merital in Sweden following a report from the Swedish regulatory authority that the incidence of certain immune reactions to the drug was unacceptably high. If the agency required sponsors to submit such evaluative material obtained from foreign regulatory bodies, it could be

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efit from learning how other regulators perceive and handle potentially important aspects of a new drug under review.

4. HOECHST DID NOT REPORT TO FDA IMPORTANT INFORMATION PERTINENT TO THE SAFETY OF MERITAL

Prior to Merital's approval, Hoechst failed to disclose to FDA information concerning the nature, extent, and severity of the drug's toxicity to the human immune system and, in the process, rendered the drug, especially as originally labeled, misbranded within the meaning of the law.

A. Hoechst Did Not Report Serious Merital-Associated Adverse Reactions Prior to the Drug's Approval

At the time of the subcommittee's hearing, FDA regulations required sponsors to supply the agency with prompt reports of "any finding" associated with a new drug under investigation "that may suggest significant hazards, contraindications, side effects, and precautions pertinent to the safety of the drug." The subcommittee's investigation revealed that Hoechst failed to report to FDA at least 30 Merital-associated deaths known to it prior to the drug's approval, four of which involved hemolytic anemia.

FDA testified that it had received *no* reports of Merital-associated hemolytic anemia fatalities until April 1985, several months following the drug's approval. Initial reports of such deaths prompted a major labeling revision in mid-1985 that emphasized the drug's capacity to induce life-threatening hemolytic anemia reactions. At the very least, Hoechst's failure to reflect Merital's potential to induce hemolytic anemia fatalities in the drug's originally approved labeling rendered the drug misbranded within the meaning of the Food, Drug, and Cosmetic Act.

On June 13, 1986, the subcommittee informed FDA of five other Merital-associated deaths that may have involved allergic reactions to the drug that were *known to Hoechst* prior to the drug's approval *but were not reported* to FDA until *after* approval. Hoechst also failed to report prior to Merital's approval at least three deaths involving cardiac complications and ten cases of drug-associated suicide and/or fatal overdose.

Hoechst also neglected to report to FDA, prior to the drug's approval, large numbers of serious, nonfatal hemolytic anemia reactions. Hoechst cited the marked increase from 1984 to 1985 in numbers of reports of hemolytic anemia cases from abroad as the principal reason for withdrawing the drug from worldwide distribution. Had Hoechst reported all such cases known to it prior to approval, a similarly marked increase from worldwide marketing experience with the drug would have been observable for 1984 as compared to 1983.

Some of the reports of Merital-associated adverse effects that the sponsor did make to FDA before the drug was approved were delayed for several years.

Some of Hoechst's adverse reaction reports to FDA did not include important records in the firm's possession. In addition, Hoechst sometimes reported adverse effects to FDA in a manner

that plainly indicated that it was not sharing all relevant information in its custody with the agency.

B. Hoechst Did Not Comply With the Adverse Reaction Reporting Requirements for Approved New Drugs

FDA regulations require that serious and unexpected (i.e., not listed in a drug's current labeling) adverse reactions associated with use of *approved* new drugs be reported to FDA within 15 working days of their initial receipt. *Fifteen-day alert reports* of serious and unexpected adverse experiences associated with use of Merital outside the United States rarely arrived at FDA on time. The agency, however, took no regulatory action in connection with Hoechst's failure to meet 15-day reporting requirements.

FDA does not require 15-day alert reports for drug-associated deaths if they are not "unexpected"; that is, if the drug's labeling acknowledges the drug's potential to induce such deaths. Thus, the sponsor did not make FDA aware of a hemolytic anemia-related death that occurred during the drug's brief and limited marketing in the United States until after Merital was withdrawn from the market. In view of its oft-stated concern with Merital's capacity to induce fatal hemolytic reactions, FDA would obviously have benefited from being promptly alerted to this death.

FDA regulations require that all domestic reports of serious adverse drug reactions for a recently approved new drug that are not subject to the 15-day alert requirement (i.e., serious but expected reactions) be included in *quarterly reports* submitted to the agency. At least 100 reports of Merital-associated adverse effects known to the sponsor during the third quarter of 1985 were not provided to FDA until the sponsor submitted its report for the fourth quarter of 1985.

FDA's regulations unwisely exempt sponsors from reporting serious but expected adverse reactions associated with the *foreign* marketing of a new drug. Once fatal hemolytic anemia became an expected (i.e., labeled) side effect of Merital therapy, the sponsor was no longer required to inform FDA of any such cases occurring during foreign marketing of the drug. Thus, Hoechst did not violate agency regulations in failing to inform FDA prior to withdrawing Merital from the market on January 21, 1986, of three drug-associated hemolytic anemia deaths occurring outside the United States that came to its attention in late 1985.

C. Hoechst Did Not Report to FDA Laboratory Study Results Revealing That Merital Was Highly Immunogenic

When Hoechst was advised in 1982 that several Swiss scientists had frequently detected drug-specific antibodies in the blood o Merital patients, the firm did not bring this matter to FDA's atten tion. On December 3, 1983, these Swiss scientists reported some o their antibody findings in a Swiss medical journal. Neither a trans lation of that German language paper, nor even a copy of it, wa ever submitted to FDA. Instead, the title of the paper was merel listed without emphasis as the 94th of 97 literature references ir cluded in a December 11, 1984, annual report to the Merital INI days before the Merital NDA was approved.

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On August 22, 1985, two German authors published a paper in the *New England Journal of Medicine* which reported the detection of antibodies against Merital and/or its metabolites in the blood of 19 Merital patients who developed hemolytic anemia. Although Hoechst was informed of their findings several months before they were published, it waited until the appearance of the *New England Journal of Medicine* paper to discuss them with FDA. Yet, based on the publication of this paper, Hoechst made revisions in Merital's labeling.

Throughout most of the review of the Merital NDA, Hoechst reported the various clinical manifestations of the drug's allergenicity as separate and discrete aspects of the drug's toxicity without any reference to the probability that they shared a common immunological origin. In fact, Hoechst repeatedly implied that no such immunological link among various drug-associated adverse effects existed.

5. FDA'S ENFORCEMENT OF THE ADVERSE REACTION REPORTING REQUIREMENTS WAS INADEQUATE

FDA administrative files contain abundant support for the committee's conclusion that Hoechst did not comply with a wide array of agency reporting requirements. Although several Hoechst submissions plainly revealed evidence of the firm's noncompliance with these requirements, FDA testified before the subcommittee that it did not recognize the sponsor "as being out of compliance."

FDA reviewers, prior to approving Merital, suspected that the sponsor had not supplied important safety information in a sufficiently timely manner. Yet, no agency investigation was ever undertaken of the sponsor's reporting practices.

In an earlier report on FDA's regulation of the arthritis drug, Oraflex, the committee concluded that the agency "places the public's health at risk when it does not vigorously enforce" requirements designed to ensure that it receives all information "needed to weigh the risks of [a new] drug against it purported benefits." FDA's continuing evasion of its law enforcement responsibilities undermines public confidence that the agency is ensuring receipt of all the information it needs to make responsible assessments of the risks of new drugs.

In its appearance before the subcommittee, FDA equivocated as to whether Hoechst was legally obligated to report to it large numbers of adverse reactions it is now known to have withheld from FDA prior to Merital's approval. This view of law enforcement is unacceptable. The legal requirement that a sponsor report all significant adverse reactions to a new drug under clinical investigation is designed to ensure that FDA receives all the information it needs to assess a new drug's risks prior to determining whether it may be approved for marketing. By publicly minimizing, after approval, the significance of large numbers of reports of potentially serious adverse drug reactions that it was not permitted to review before approval, FDA signals to sponsors that they need not ensure that FDA's decisions reflect all potentially relevant safety data in their possession.

For some reason, FDA was also reluctant to acknowledge tha agency reporting requirements had been violated in connectio with the sponsor's failure to inform it that Merital had been foun to be highly immunogenic. FDA testified that such information wa "pertinent" and "should [have been] submitted," but that it wa "not sure [such information] would have made any difference t [its] conclusions about the drug." Accordingly, FDA maintaine that such information *may not* have been required to be reporte

The committee finds it disturbing that FDA would take a publ position that possibly excuses a drug sponsor from informing it data that suggested the drug's potential to induce allergic rea tions.

Section 505 of the Food, Drug, and Cosmetic Act requires "*fu reports* of investigations which have been made to show whether not such drug is safe for use . . ." (Emphasis supplied.) The la clearly did not contemplate public speculation by FDA officia after approval on the significance of test data they never had th opportunity to review before approval.

The committee believes that FDA's policies and public stat ments should make clear that the "full reports" requirement of th Food, Drug, and Cosmetic Act places the legal burden on sponso to ensure that the agency has an opportunity to conduct an inc pendent review of all investigations that could possibly bear on t safety and efficacy of a new drug under review.

6. THE EFFICACY OF MERITAL WAS NOT SUPPORTED BY SUBSTANTI EVIDENCE DERIVED FROM ADEQUATE AND WELL-CONTROLLED STUDI AS REQUIRED BY LAW

In enacting the Drug Amendments of 1962, Congress effective declared that FDA should not permit public exposure to the ris of *any* new drug, until, at the very least, its sponsor has provid "substantial evidence . . . consisting of adequate and well-controll investigations . . . that the drug will have the effect it purports is represented to have under the conditions of use prescribed, r ommended, or suggested in the labeling or proposed labeling the of." The committee's review indicates that FDA permitted t public to be exposed to an unusual panoply of risks presented Merital without assurance that the drug's efficacy was support by "substantial evidence." In this regard, FDA failed to perform responsibilities under the law.

FDA has consistently interpreted the law to require, as a p condition for NDA approval, that efficacy be demonstrated by least *two* adequate and well-controlled studies. FDA cited th clinical trials—known as the Georgia, Meredith, and Varga st ies—as the basis for its conclusion that Merital was an effective tidepressant.

FDA's statistician, however, testified that two of these studie Varga and Georgia—did not provide substantial evidence of M tal's efficacy. Thus, in his estimation, the drug's efficacy was supported by at least two adequate and well-controlled studies, required by law and established agency policy.

Only 26 patients received Merital in the Varga and Georgia st ies, 7 and 19, respectively. Early in the review of the Merital NI

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FDA cited these small numbers in concluding that these trials could not serve as "pivotal" evidence of the drug's efficacy.

Later FDA defended its subsequent reliance on these trials by emphasizing that they yielded statistically significant results in favor of Merital. This argument evades what had been the agency's principal concern with their small numbers; namely, that such small patient samples may not be representative of the universe of depressed patients for whom the drug was indicated.

Further limiting the representativeness of the Varga and Georgia studies was the restricted nature of their patient populations. The Varga study included only geriatric patients and the Georgia study consisted almost entirely of male patients. FDA reviewers stated on several occasions that the types of patients participating in these studies were insufficiently representative of the universe of depressed patients for whom the drug was indicated.

FDA stated in the Summary Basis of Approval for Merital that "analyses" of the NDA indicated that gender and age were not related to the outcome of the Varga and Georgia studies. FDA, however, never performed any such "analyses." Nor did any agency medical review detail the agency's rationale for concluding that Varga and Georgia study results were applicable to the non-elderly and women, respectively.

FDA's clinical reviewer ultimately decided that Merital had "a mild antidepressant effect" and wrote that "a more effective antidepressant should produce less equivocal results." FDA's statistician testified that if Merital has only a mild antidepressant effect, larger studies should have been done to document that effectiveness. None of the larger Merital studies demonstrated the drug to be significantly better than placebo.

Approximately *80 percent* of the placebo-controlled studies involving Merital did not demonstrate the drug's superiority to placebo. In some studies, placebo outperformed Merital, with one study showing the statistically significant superiority of placebo to Merital. A "substantial evidence" test cannot be met where the overwhelming majority of studies either demonstrate no statistically significant superiority to placebo or inferiority to placebo. In fact, Dr. Paul Leber, Director, FDA's Division of Neuropharmacological Drug Products, had advised the sponsor in January 1983 that "the studies yielded so many divergent results we do not have convincing evidence of efficacy before us which would allow us to approve the drug."

FDA argued that in five of six three-way studies comparing imipramine—a standard, approved antidepressant—as well as Merital with a placebo treatment, neither imipramine nor Merital outperformed placebo. FDA testified that negative studies in which imipramine—presumably an effective antidepressant—also did not outperform placebo represent "failed studies" rather than evidence *against* Merital's effectiveness.

The law requires proof of effectiveness. It is not FDA's responsibility to *assume effectiveness*, even of an approved drug such as imipramine, where a particular study does not support effectiveness. That imipramine did not fare better than placebo does not prove that Merital has been shown to be effective.

The only three-way study that FDA did not regard as "faile was the Varga study, a trial whose small sample size and exclusiv ly geriatric make-up rendered it, in the judgment of several agen reviewers, inadequate as representative evidence of Merital's an depressant efficacy.

In addition, at least six negative placebo-controlled studies we two-way, not three-way trials. In arguing that negative studies re resent "failed" studies and not evidence against the effectiveness Merital, FDA *assumed* that the results of five three-way stud were applicable to these other negative placebo-controlled trials.

The legal burden for demonstrating efficacy is on the sponsor. is inappropriate for FDA to make assumptions that explain aw several negative studies performed for the drug.

Subsequent to the subcommittee's May 22, 1986, hearing, FI approved another drug, despite several negative efficacy stud submitted for it, including three-way studies in which an alrea approved drug outperformed placebo. This drug was approved ev though it failed the test presented by FDA as the one reason th negative results in the Merital clinical trials program could be c regarded.

In approving Merital, FDA concluded that the evidence of its fectiveness was "modest." No reasonable construction of "substa tial evidence" could embrace evidence that the agency concedes "modest." Moreover, the record of the agency's review of the effi cy data is replete with statements that the sponsor had not su plied "substantial evidence" of Merital's antidepressant effica Dr. Paul Leber, Director, FDA's Division of Neuropharmacologi Drug Products told the sponsor in 1982 and 1983 that he h "severe doubts of whether the drug is an effective antidepressa and that "[w]e would be troubled if this drug were approved wh effective drugs are available."

In January 1983, Dr. Leber advised the sponsor that "[w]e can conclude the drug is effective based on studies presented to dat Nonetheless, the agency's decision to declare Merital effective v based on studies included in the original NDA submission of cember 1978. In view of the agency's persistent reservations ab whether "substantial evidence" of efficacy had been demonstrat the committee sees no basis for FDA's failure to condition appro on the sponsor's submission of new efficacy studies *clearly dem strating* the drug's efficacy in depressed patients.

Dr. Leber testified that at one point during its review of the M ital NDA, FDA tried "to figure out how to approve this drug." T demonstrates a serious misunderstanding of FDA's function. C gress did not authorize FDA, in its review of new drug applicatic to engage in any function other than assuring that sponsors h demonstrated new drugs *safe and effective* within the meaning the law. The agency has not been delegated the responsibility try to figure out how to approve" new drugs whose efficacy is s ported by evidence of very dubious value.

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7. FDA'S APPROVAL OF MERITAL WAS DRIVEN BY ITS DETERMINATION TO MEET INAPPROPRIATE END-OF-THE-YEAR DEADLINES

Record numbers of new drug approvals in recent years, which FDA cites as evidence of progress in improving new drug review procedures, have been made possible by large numbers of approvals in the month of December. FDA maintains that the flurry of activity in December reflects companies' desire to meet end-of-the-year deadlines rather than an FDA program to improve yearly scorecards.

The record in the Merital case, however, suggests otherwise. FDA abruptly dropped its previous insistence that Meri[illegible]e marketed only as "second-line" therapy in late December 1[illegible]and informed Hoechst that it was determined to approve the drug by year's end. Hoechst saw this as a "concession" that satisfied its "minimal needs for a marketable drug."

FDA is prohibited by law from approving new drugs unless they have been shown to be safe and effective and their labeling bears adequate directions for use. It is imperative that the agency ensure that its approval actions are not influenced by arbitrary, self-imposed, end-of-the-year deadlines.

IV. DISCUSSIONS

1. PRIOR TO APPROVING MERITAL, FDA OVERLOOKED EVIDENCE OF THE DRUG'S ALLERGY-INDUCING POTENTIAL

Prior to its approval, Merital was associated with reports of various combinations of signs and symptoms, including eosinophilia (an abnormally high count of a certain kind of white blood cells); fever, including hyperpyrexia (or extremely elevated fever); arthralgia (joint pain); myalgia (muscle pain); skin rashes, including urticaria (hives); abnormal liver functioning, including granulomatous hepatitis and jaundice; hemolytic anemia (destruction of red blood cells), sometimes accompanied by kidney failure; thrombocytopenia (depressed blood platelet counts); and pulmonary or lung infiltrates.

N. Franklin Adkinson, M.D., an Associate Professor of Medicine with a joint appointment in the Subdepartment of Immunology of The Johns Hopkins University School of Medicine, testified at the subcommittee hearing that reports of such reactions indicated that Merital clearly produced immune reactions; that is, it was an allergy-inducing or allergenic drug:

> There is no question but that Merital was reported to have induced a wide variety of adverse effects which are generally considered to be potentially of immunologic origin. . . . There were cases of hyperpyrexia, or high fever,[102] a granulomatous form of hepatitis,[103] immune cytolysis [destruction] of both red cells [i.e., hemolytic anemia] and platelets [i.e., thrombocytopenial], vasculitis [inflammation of the peripheral blood vessels], alveolitis [inflammation of the small airsacs of the lung],[104] renal failure in some cases secondary to intravascular hemolysis and eosinophilia[105] and more rarely, rash.[106]

Drug allergy is generally diagnosed on the basis of drug-assoc[illegible]ed signs and symptoms that are presumed to be allergic or imm[illegible]ologic in nature.[107] Reports to FDA before Merital's approval [illegible]cluded most of the limited number of manifestations frequently [illegible]sociated with drug allergy, including skin rashes, serum sickn[illegible] unexpected fever, eosinophilic pulmonary infiltrates, anen[illegible] thrombocytopenia, and liver damage.[108]

Noted experts in drug-induced immune reactions who were c[illegible]sulted by the subcommittee concurred with Dr. Adkinson's ass[illegible]ment that, prior to Merital's approval, a number of adverse eff[illegible] reported for the drug were presumably allergic in nature.[109]

In Dr. Adkinson's judgment, a "common immunologic orig[illegible] linked various combinations of signs and symptoms such as he[illegible] lytic anemia, fever, eosinophilia, and liver function abnormalit[illegible] that were reported for Merital.[110] Shortly before Merital was [illegible]proved, the sponsor acknowledged Merital's probable associat[illegible] with such an immune syndrome or group of syndromes. In an O[illegible]ber 29, 1984, submission to FDA, the sponsor stated that, collect[illegible]

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[102] Dr. Adkinson testified that the most common mechanism of drug fever is probably im[illegible] ologic, "particularly in drug fevers that arise late in the course of therapy." Hearing, pa[illegible] Fever, in Dr. Adkinson's estimation, was "one of the most frequently reported side effec[illegible] the drug." Hearing, page 6. In fact, the reported incidence of Merital-associated fever ofte[illegible] peared greater than the 1 percent incidence claimed by the sponsor. For example, a Har[illegible] Medical School physician reported, in an April 9, 1985, letter to Hoechst, a 17-percent fever[illegible] dence among the patients whom he treated with Merital. In subcommittee files.

[103] Dr. Adkinson testified that growths called granulomatous lesions found in the livers o[illegible] tients, particularly in those "who have no history of alcohol abuse," could indicate a hypers[illegible] tivity reaction. Hearing, page 6. He testified that he reviewed a 1977 report of such lesions[illegible] the U.S. clinical trials. A case of Merital-associated granulomatous hepatitis was also rep[illegible] in a 1980 Swiss article he reviewed. He observed additional reports of granulomatous liv[illegible] sions in a July 22, 1981, report to the Merital IND. Hearing, pages 6-7.

[104] Dr. Adkinson noted, for example, a case of fever and allergic alveolitis reported in a [illegible] paper in the Swiss literature. Hearing, page 6.

[105] Dr. Adkinson testified that "in most cases elevated eosinophil in the blood indicate a[illegible] going inflammatory or allergic or immunologic reaction of some type of another." Hearing, [illegible] 6. Dr. Adkinson testified that abnormally high eosinophil counts were frequently reporte[illegible] Merital; the sponsor's U.S. clinical trial data showed an eosinophilia incidence of approxim[illegible] 15 percent. Hearing, page 6.

[106] Hearing, page 5.

[107] In a July 14, 1986, letter to the subcommittee, Dr. Richard D. deShazo, Professor of M[illegible] cine and Pediatrics and a member of the Section of Clinical Immunology and Allergy, Tu[illegible] University Medical Center, wrote: "[F]or the present one must discuss drug hypersensit[illegible] more on the basis of the common sense and deductive reasoning rather than on the bas[illegible] science. If a given drug repeatedly gives reactions which have the clinical characteristics a[illegible] ated with hypersensitivity reactions, one must assume that (1) the drug is causing the react[illegible] and (2) the reactions are immunologically mediated." In subcommittee files.

[108] These side effects are included among the "clinical features of drug hypersensiti[illegible] which according to the 13th edition of the Merck Manual (1977), "are restricted in their [illegible] festations." See pages 237-8.

[109] These included Dr. Richard D. deShazo, Professor of Medicine and Pediatrics, and me[illegible] of the Section on Clinical Immunology and Allergy, Tulane University Medical Center; Dr. [illegible] dell F. Rosse, a Professor of Medicine and immuno-hematologist at the Duke University Me[illegible] Center, and Dr. Paul P. VanArsdel, Jr., Professor of Medicine and Head, Section of Allergy [illegible] School of Medicine, University of Washington. Their letters to the subcommittee are in sub[illegible] mittee files.

[110] Hearing, page 7.

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ly, Merital-associated hemolytic anemia, fever, eosinophilia, and liver function abnormalities, "probably reflect different target organ sensitivities to a *single immunological event*." [111] (Emphasis supplied.)

In a May 1985 submission, Hoechst stated that physicians "should be aware" of such "hypersensitivity reaction[s] to Merital," [112] but the labeling originally approved by FDA a few months earlier did not warn physicians that several signs and symptoms reported for Merital probably reflected various manifestations of a "single immunological event," or immune syndrome or group of syndromes. In this connection, Dr. Adkinson testified that while "the various adverse reactions attributed to Merital were certainly contained in the package insert, . . . there was no effort to put these various immune disorders together and to suggest what I think was apparent at that time, that there was a common immunologic basis for these based upon the drug's significant immunogenic potential."[113] In short, Dr. Adkinson testified, the original Merital labeling contained no warning that serious reactions such as hemolytic anemia probably constituted part of a Merital-induced immune syndrome or group of syndromes.[114]

Despite Dr. Paul Leber's statement before the subcommittee that FDA was fully aware of the possibility that several reactions induced by the drug had a common immunological basis,[115] Dr. Robert Temple, Director, FDA's Office of Drug Research and Review, testified to the contrary:

> I don't think that I disagree with [Dr. Adkinson] as far as his factual statements about the reactions that were seen or the immunological findings. . . . It may well be, especially after the fact, completely obvious that all of the adverse reactions to nomifensine, such as eosinophilia (which isn't really an adverse reaction but rather a laboratory observation), the febrile syndrome, and so on, *can be, and perhaps should earlier have been, recognized as all related to immune complex formation*.[116] (Emphasis supplied.)

Although *conceding that* FDA failed to recognize the immunological origin of several Merital-associated adverse reactions, Dr. Temple maintained that such recognition was not relevant to the agency's consideration whether and how Merital could be safely used:

> . . . Such recognition . . . doesn't tell you what to do about the reactions. It merely helps explain them. What is of interest is how commonly they occur, how severe they

[111] Hearing, page 7.
[112] See Hoechst's draft Product Monograph that was submitted to FDA on May 20, 1985, in subcommittee files.
[113] Hearing, page 7.
[114] Ibid.
[115] Dr. Leber testified:

> The question, in 1984 when we made the approval was whether or not we had enough information to reach a conclusion about a linkage between a variety of syndromes and then stress this hypothesis in nomifensine's labeling. . . . It's not that we were unaware; it's that we were not convinced. Hearing, page 17.

[116] Hearing, page 16.

> are when they do occur, how the frequency and severity compare to alternative therapies, and the extent to which they provoke concern. . . . The mechanism is really not relevant except to the extent it predicts how common or severe the damage will be. . . . [W]hat's really important is what the damage is to patients, not the mechanism. . . . It doesn't matter what the mechanism is. It matters what it does.[117]

By definition *allergic* drug reactions "involve an immunologic mechanism."[118] In minimizing the significance of the "immuno gical mechanisms responsible for many reported drug-associat signs and symptoms, Dr. Temple's testimony confirms a central ficiency in FDA's pre-market regulation of Merital's safe namely, the agency's failure to recognize the drug's significant tential to induce *allergic* reactions.

A review of the relevant and extensive medical literature on t clinical diagnosis and management of drug-induced allergic dis ders directly contradicts FDA's position that recognition of Me tal's capacity to induce immunologically mediated or allergic re tions was unimportant. For example, one commentator has writte "Although most patients with a history of reacting to a drug cou safely receive that drug again, the outcome could be serious if t individual is truly allergic."[119] Allergic drug reactions, unli other toxic drug effects, can be precipitated by minute amounts a drug, far below therapeutic doses.[120] Thus, another expert h written:

> As a rule, there is a risk that even small doses will produce the reaction again. Hence, the modest dose reduction that might be used to prevent toxic reactions would be ineffective and even dangerous for preventing an allergic reaction.[121]

Accordingly, allergy experts agree that allergenic drugs shou be discontinued in patients known to be sensitive to them if ther peutic alternatives are available [122] to avoid the possibility injury upon re-exposure. As Dr. Adkinson has written:

> Discontinuation of the sensitizing drug, and indefinite suspension of its use, is indicated in almost all immunologic drug reactions.[123]

[117] Hearing, pages 16 and 24.
[118] See Adkinson and Lichtenstein, "Techniques of Assessing the Immune Response Drugs," *Drug Design and Adverse Reactions*, ed. Bundgaard, et al., Munksgaard, Copenhag page 123.
[119] Richard D. DeSwarte, "Drug Allergy," in *Allergic Diseases: Diagnosis and Manageme* ed. Roy Patterson, 3d ed., J. B. Lippincott Co., Philadelphia, 1985, p. 507.
[120] See Kenneth W. Witte and Dennis P. West, "Immunology of Adverse Drug Reaction *The Journal of Human Pharmacology and Drug Therapy*, vol. 2, No. 1, January/February 19 Also see VanArsdel, "Adverse Drug Reactions," in *Allergy: Principles and Practices*, supra, pa 1390.
[121] See Paul P. VanArsdel, Jr., "Diagnosing Drug Allergy," Journal of the American Medi Association, vol. 247, No. 18, page 2576.
[122] "Ordinarily, a history of allergy to any drug indicates that the drug should not be used an alternative drug of different chemical structure is likely to be as effective." See Paul P. V Arsdel, Jr., M.D., "Adverse Drug Reactions," in *Allergy: Principles and Practices*, supra, pa 1408.
[123] N. Franklin Adkinson, "Adverse Drug Reactions," *Current Therapy*, ed. by Howard Conn, page 599.

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Allergic drug reactions usually occur upon re-exposure to a drug after a previous period of use and sensitization. Dr. Adkinson testified that "[t]here must be an initial exposure to sensitize the patient and after which either continued exposure or re-administration at some later time is capable of initiating an adverse immunologic event.[124] Many allergic reactions to Merital followed this course.[125] To the extent that depressed patients are often likely to use an antidepressant episodically, any serious reaction that can occur upon re-exposure to an allergenic drug is certainly germain to assessing whether or how it can be safely used.

In this connection, a letter to the *British Medical Journal* discussed a patient who, re-experiencing depression after several months off Merital, took two tablets of the drug from those remaining from her original prescription, after which she experienced intravascular hemolysis and renal failure. The authors concluded:

> This case highlights the dangers of immune mediated drug reactions, particularly with psychotropic agents, where patient compliance may be unpredictable and subsequent re-exposure may occur after hoarding.[126]

Recognition that Merital induced an immune syndrome or syndromes was also important because serious reactions were often preceded by more benign allergic responses occurring upon one or more prior exposures.[127]

Awareness that an initial, relatively benign allergic reaction, such as fever, may eventually lead to more severe allergic reactions is essential to early detection and clinical management of potential, drug-induced allergic disorders. In the words of one expert:

> Because drug fever commonly precedes the development of more serious manifestations (for example, drug-induced hepatitis, vasculitis, hematologic reactions, and exfolitative dermatitis), its recognition is imperative.[128]

The European medical literature in early 1985 warned of the need to heed such early reactions. For example, in February 1985,

[124] Hearing, page 4.

[125] For example, of 11 patients who developed hemolytic anemia whose cases were analyzed by Hoechst, 9 had a history of terminated prior exposure to Merital. Usually, one to two capsules upon retreatment would precipitate the hemolytic episodes. See the memorandum by Aleta Sindelar of FDA of a June 5, 1984, telephone conversation with Mr. Dennis Bucceri and Dr. Charles Thayer of Hoechst's U.S. affiliate, which is in subcommittee files.

Additional examples of this phenomenon abound. Severe hemolysis accompanied by renal failure occurred in two cases following resumption of medication with one capsule of Merital after a period off the drug. See Eckstein, et al., "Immune Hemolytic Anemia and Renal Failure After Nomifensine," *Klinische Wochenschrift*, vol. 59, 1981, pages 567-9. Similarly, on June 13, 1986, Hoechst reported to FDA a case involving a 32-year-old Ohio woman who had previously used Merital in August 1985. Three or four hours after taking one dose of the drug on May 10, 1986, she presented at an emergency room with hemolytic anemia, coagulation disorder, and acute renal failure. She subsequently had to undergo dialysis. In subcommittee files.

[126] A.R. Morton, et al. *British Medical Journal*, August 16, 1986, Vol. 293.

[127] For example, the July 14, 1979, *Lancet* reported on a patient who had experienced seven previous, identical episodes of fever accompanied by malaise, chills, and abdominal pain before developing hemolytic anemia. F. Bournerias, B. Habibi, "Nomifensine-Induced Immune Haemolytic Anemia and Impaired Renal Function," pages 95-6. Similarly, a French patient developed high fever on her 16th day on Merital, accompanied by chills, cutaneous eruptions, agitations, and delirium. The drug was discontinued and the fever resolved promptly. Fever recurred when the drug was restarted and, four days later, she was found to have developed acute hemolytic anemia. The report of this 1982 case was included in an October 29, 1984, submission to FDA, which is in subcommittee files.

[128] See DeSwarte, supra, page 535.

a German medical publication, the Arznei-telegramm, after notin that "nomifensine can induce an immune-allergic reaction, whic usually manifests itself . . . in fever, serum sickness-like con plaints with muscle aches, joint pain and flu symptoms [that] ca proceed [to] blood damage (thrombocytopenia) and pathologic liver function including granulomatous hepatitis, [and] bronch pneumonia," concluded that "the threatening clinical picture the immune allergic reaction requires the immediate discontin ation of treatment with the occurrence of symptoms such as fev or flu."[129]

In a similar vein, the Drug Commission of the German Medic Profession issued the following warning on March 27, 1985:

> The Drug Commission, therefore, advises all physicians, even as early as the occurrence of fever, to discontinue nomifensine immediately. . . .[130]

Since FDA apparently did not appreciate the significance of t clinical manifestations of Merital's allergenicity prior to approvi the drug, nothing in the drug's original labeling, or, in the labeli for the drug when it was launched in the U.S. in July 1985, alert physicians to the "threatening clinical picture of the immune all gic reaction" necessitating "immediate discontinuation of tre ment with the occurrence of symptoms such as fever or flu."[1] The committee concludes that FDA, in failing to ensure that t original labeling for Merital bore "adequate directions for use" including such a warning, did not prevent the drug from being m branded within the meaning of §502(f) of the Food, Drug, and C metic Act.

FDA's attempts to minimize the significance of Merital's all genic potential was inconsistent with the manner in which it h regulated new drugs in the past. In its regulation of the nonste dal anti-inflammatory drug, Zomax (zomepirac sodium), for exa ple, FDA believed that physicians should be warned of the possib ty of mild immunological reactions that could foreshadow m severe allergic reactions upon re-exposure to Zomax.[132]

[129] In subcommittee files. Translated from the German. The *Drug and Therapeutics Bul* similarly noted on December 16, 1985:

> Since the reactions cannot be predicted or prevented in patients on nomifensine, they must be detected early and the drug stopped at the first suspicion. Patients should therefore be told to stop the drug and see the doctor if they feel physically unwell, o develop fever or aches and pains. Patients who have stopped taking the drug should b warned against starting it again since this could lead to an immediate reaction. . . Any doctor looking after a patient on nomifensine will need to keep careful watch fo the serious reactions this drug may cause, and should withdraw the drug at the firs sign of trouble.

"Trouble with nomifensine," *Drug and Therapeutics Bulletin*, Vol. 23, No. 25, pages 98-100.

[130] Translated from the German. The March 27, 1985, issue of the *Deutches Arzteblatt* subcommittee files.

[131] It was not until November 13, 1985, that Hoechst advised FDA that "Merital shou discontinued in patients developing any degree of fever" and that it was modifying the labeling to state this. See the November 13, 1985, letter from Mr. Dennis Bucceri, Vice Pres Regulatory Affairs of Hoechst's U.S. affiliate, to Dr. Paul Leber, in subcommittee files.

[132] In hearings before the subcommittee on the regulation of Zomax on April 26, 1983, testified that, because individuals who had a mild allergic reaction to Zomax on previous sure to the drug were at higher risk for a severe allergic reaction, the sponsor of Zoma correct to warn physicians that "[w]hen represcribing Zomax, you should be particularly a mild [allergic] reactions that the patient may have experienced while taking the drug pre ly." Hearings before a Subcommittee of the Committee on Government Operations, Ho Representatives, "FDA's Regulation of Zomax," April 26 and 27, 1983, pages 110-111.

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Notwithstanding FDA's testimony before the subcommittee minimizing the significance of the immunological basis for much of Merital's toxicity, FDA did eventually conclude, shortly before the drug was removed from the market, that an immunological link existed for many Merital-associated adverse effects, and that Hoechst should relabel the drug to emphasize this. So, nearly one year *after* FDA approved Merital for marketing, it recommended at a November 8, 1985, meeting with Hoechst that the company restructure the warning section of Merital's labeling.[133] Dr. Temple testified that, as a consequence of that meeting:

> . . . the labeling was revised to convey our altered impression of the . . . type of risk associated with Merital's use as well as the underlying mechanism we thought might link them. . . . Essentially, the immune mediated nature of the several reactions was highlighted in an introductory paragraph of the Warnings Section, and hemolytic anemia was placed at the top of the list of those disorders of presumed immune pathogenesis.[134]

In addition to acknowledging that such a change was "essential to maintain[ing] [the] accuracy" of Merital's labeling, Dr. Paul Leber wrote in an August 5, 1986, memorandum that "[i]dentifying a more generalized immunopathogenetic risk factor was seen as a *means of sensitizing prescribers to the potential for a type of risk that might easily be unappreciated or overlooked.*" [135] (Emphasis supplied.)

The Detection of Drug-Specific Antibodies in an Extraordinarily High Percentage of Merital Patients Further Evidenced the Drug's Allergenic Potential

Antibodies are proteins produced by the body in response to a foreign substance such as a drug that can recognize and, in some cases, react with that substance to induce an allergic reaction.[136]

Dr. Adkinson testified that the development of antibodies to Merital or its metabolites—that is, its breakdown products in the body—could lead to life-threatening adverse reactions in some instances.[137] He stated, for example, that the "likely mechanism" of Merital-induced immune hemolytic anemia was "one of union of antibody with the drug, in this case Merital which it recognized, resulting in an immune complex which was toxic to nearby red blood cells and resulted in their lysis or prompt removal from the circulation." [138]

[133] According to a November 13, 1985, letter to FDA from Hoechst, this change was made at the recommendation of Dr. Paul Leber. See the subcommittee's July 14, 1986, letter to FDA, Hearing, page 446.

[134] Hearing, pages 13-14. Thus the warning section opened as follows:

> *Immune mediated injury*
>
> Illnesses that may be caused by immune mediated injury have been reported in association with the use of Merital (nomifensine maleate). These include hemolytic anemia, a syndrome of fever and alveolitis (which has been linked causally to nomifensine by positive rechallenge) eosinophilia, necrotizing vasculitis and a lupus like syndrome. These illnesses can produce significant morbidity and fatal cases have been reported.

[135] In subcommittee files.

[136] Hearing, page 4.

[137] Hearing, page 4.

[138] Hearing, page 4.

A person developing antibodies against a drug exhibits sensitivity, or a specific "immune response," to it. Dr. Adkinson has written that *allergic reactions* are adverse effects that can be attributed directly to such an immune response.[139] Thus, tests for allergic drug reactions are often directed at detecting the presence of drug specific antibodies in a patient's blood.[140]

The December 3, 1983, issue of *Schweizerische Medizinische Wochenschrift* (hereafter referred to as the *Swiss Medical Weekly*) reported an antibody study of 51 patients who received Merital, 41 of whom had exhibited adverse reactions to the drug [141] and ten of whom were asymptomatic. Merital was reported to be *highly immunogenic*; that is, it was found to be associated with a high degree of drug-specific antibody formation. Antibodies to Merital and/or its metabolites were detected in *all 51 Merital patients* whose blood was tested.[142] By contrast, all eight control patients who did not receive the drug did not develop Merital-specific antibodies. Subsequent work by the authors revealed that approximately 88 percent of a total of 105 persons given Merital developed drug-specific antibodies.[143]

Dr. Adkinson testified that the degree of drug-specific antibody formation associated with Merital may have been unique: "I'm not aware of any currently marketed drug that induces antibody in such a high percentage of patients." [144]

In an October 29, 1984, submission to FDA, Hoechst included an August 23, 1984, letter from a hematological consultant, Dr. S. Sherry, Dean of the School of Medicine at Temple University. Based on materials provided him by Hoechst, Dr. Sherry noted in his letter that "[a]ll patients on prolonged therapy develop . . . antibodies to the drug." [145] Despite receipt of this letter, it was not until the subcommittee's May 22, 1986, hearing that FDA learned that Merital had been reported to be *highly immunogenic.*

As earlier discussed, Dr. Robert Temple, Director, FDA's Office of Drug Research and Review, testified before the subcommittee that, in the absence of data relating antibody formation to adverse reactions, antibody formation was of little clinical significance in that it provided information only on the "mechanism" for particular reactions, which "is really not relevant except to the extent it predicts how common or severe the damage will be." [146] Thus, the antibody findings for a drug like Merital, Dr. Temple concluded, "wouldn't particularly have a major implication for me unless I knew what the consequence of that was." [147]

[139] N. Franklin Adkinson, "Adverse Drug Reactions," *Current Therapy*, ed. Howard F. Co 1977, page 599.

[140] N. Franklin Adkinson, "Tests for Immunological Drug Reactions," *Manual of Clinical Immunology*, 2d edition, American Society for Microbiology, Washington, D.C., 1980, page 822.

[141] These included seven cases of hemolytic anemia, two cases of allergic alveolitis, ten cases of hepatitis with fever, and twenty-two cases of fever alone. Hearing, page 4.

[142] Hearing, page 4.

[143] See "Radioimmunologische Erfassung von IgE- und IgG-Antikorpern gegen Medikamente published in the *Schweizerische Medizinische Wochenschrift*, 116, 303-5 (1986). The only drug class that approached this percentage was the bioflavonoids; drug-specific IgG antibodies were found in 79 percent of the patients receiving bioflavonoids whose sera were assayed.

[144] Hearing, page 5.

[145] Hearing, page 21.

[146] Hearing, page 24.

[147] Hearing, page 23.

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Dr. Temple's statements contradict accepted principles of immunology. As Dr. Adkinson has acknowledged, a basic problem for immunology has been the frequently observed discrepancy between the capacity of a substance to induce antibodies (immunogenicity) and its capacity to induce clinically observable adverse reactions (allergenicity).[148] Knowledge that Merital was highly immunogenic would not, by itself, enable one to predict who would be at risk for an allergic reaction, or how frequent or severe allergic reactions to the drug might be. Thus, Dr. Adkinson wrote that the "fact that a drug can elicit a drug-specific immune response . . . does not mean that allergic reactions will be so prevalent as to preclude its use." [149]

However, awareness of Merital's immunogenicity would have indicated that a large percentage of those exposed to the drug did exhibit sensitivity—that is, an "immune response" to it and/or its metabolites—the significance of which would have required further investigation. By itself, the drug-specific immune response, Dr. Adkinson has observed, "indicates a *potential* adverse reactivity" [150] of an allergic nature:

> There is virtually no disagreement among scientists and physicians interested in drug allergy that drugs and chemicals which readily engender a drug-specific immune response have a greater potential for allergic drug reactions than drugs which do not stimulate the immune system.[151]

At the very least, the presence of drug-specific antibody signals a greater potential for allergic reaction than does its absence. Dr. Temple acknowledged that "[o]bviously, you don't want to form antibodies if you can help it." [152]

Dr. Adkinson testified that "[i]n a drug that has very high immunogenicity with 80 to 100 percent immune response rate, I believe with widespread administration and use of the drug, allergic drug reactions of some form can be anticipated to occur." [153] As Dr. Adkinson testified, *frequent antibody formation could signal the potential for very severe allergic reactions,* such as "anaphylactic shock, severe intravascular hemolysis, sometimes leading to kidney failure, damage to the lungs, and hepatitis. All of these latter, more severe reactions can, and have been, fatal." [154]

In the case of Merital, Dr. Adkinson observed, *the creation of antibodies could lead to very serious, even life-threatening adverse reactions if drug therapy were continued.*[155]

Dr. Adkinson has concluded that "the documented record of Merital provides an excellent case study of the *expected* consequences of widespread use of a highly immunogenic drug," [156] (emphasis

[148] Adkinson, "Drug Hypersensitivity—Prevention, Diagnosis, and Management," *Delaware Medical Journal,* Vol. 47, No. 11, page 647.
[149] Hearing, page 528.
[150] See his September 29, 1986, letter to the subcommittee, Hearing, page 528.
[151] Ibid.
[152] Hearing, page 25.
[153] Hearing, page 8.
[154] Hearing, page 5.
[155] Hearing, page 4.
[156] See his September 29, 1986, letter, Hearing, page 527.

supplied) and that it is "distress[ing] . . . that the FDA still considers the information regarding the immunogenicity of Merital and other drugs to be of incidental value." [157]

Nonetheless, Dr. Temple attempted to minimize the significance of the antibody findings for Merital by characterizing them as an isolated laboratory phenomenon:

> [I]f it is now seemingly true that this particular [immunological] mechanism carries a particular implication, maybe that is something to learn. But I don't see how one could have known that or thought that before the events happened. There are a great many drugs that form antibodies. . . . The question always is, what does [antibody formation] mean? Just forming antibodies doesn't mean anything by itself.[158]

Any suggestion that the antibody findings would have existed in a vacuum removed from reports of clinically manifest adverse experiences is belied by the record. In fact, had FDA been aware prior to approving Merital, that virtually everyone exposed to Merital experienced a drug-specific immune response, it may not have overlooked the abundant clinical evidence it received of Merital's capacity to induce a wide range of allergic reactions. As earlier noted, Dr. Temple acknowledged that "it may well be . . . completely obvious" that several signs and symptoms reported for Merital "can be and perhaps should earlier have been recognized as all related to immune complex formation." [159] Moreover, it was concern over reports in 1978 and 1979 of adverse reactions to Merital, most notably hemolytic anemia, that prompted Hoechst to sponsor antibody studies "to determine the seriousness of the problem." [160] In a January 1980 report, Hoechst described its recently initiated European Surveillance Program, under which immunologists in Germany,[161] France,[162] and the United Kingdom [163] were to investigate blood samples of Merital patients for the presence of drug-specific antibodies.

Antibody detection studies followed rather than preceded reports of adverse effects that had the clinical appearance of allergic reactions. Thus, Dr. K. Neftel, a Swiss scientist who co-authored the December 3, 1983, *Swiss Medical Weekly* article on Merital's immunogenicity, approached Hoechst in the spring of 1982 and proposed that the company supply him several blood samples from Merital patients so that he could test his theory that Merital was associated with immunological reactions. Prior to this time, Dr. Neftel had noted that Merital resembled Catergen (generic name cyanidanol), a drug marketed for the treatment of liver disease in Europe at the time, in that both drugs had been associated w

[157] Ibid.
[158] Hearing, page 24.
[159] Hearing, page 16.
[160] See Hoechst's July 7, 1980, amendment to the Merital NDA, in subcommittee files.
[161] These immunologists were affiliated with the Behring Institute in Marburg, Germany.
[162] Dr. B. Habibi of the Centre National de Transfusion Sanguine Annexe in Paris, one of authors of the July 14, 1979, report in *The Lancet* on a French case of Merital-induced immune hemolytic anemia and secondary renal failure.
[163] Dr. J. Watkins of the University of Sheffield.

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presumably allergic reactions such as hemolytic anemia[164] and fever.[165] Dr. Neftel had developed a method for detecting drug-specific antibodies in patients receiving Catergen,[166] and, because the side effects profile for that drug resembled Merital's, he proposed using the same method to investigate Merital blood samples for the presence of drug-specific antibodies.[167]

Dr. Neftel's search for Merital-specific antibodies was conducted against the background of large numbers of possibly allergic reactions that had already been reported for the drug. As Professor A. L. de Weck, a co-author of the December 3, 1983, Swiss report on Merital's immunogenicity and the Director, Institute for Clinical Immunology, Inselspital, Bern, Switzerland, advised the subcommittee on September 30, 1986:

> In the presence of . . . signs and symptoms [suggesting allergenicity] serological investigations for the presence of drug specific antibodies should certainly be taken into consideration. This is also the reason why we have undertaken them [for Merital].[168]

It is noteworthy, in this regard, that the report of some of the findings of Dr. Neftel and his colleagues in the December 3, 1983, *Swiss Medical Weekly* states:

> Side effects such as immunohemolysis with renal failure, fever and/or hepatitis, and interstitial pneumonopathy have repeatedly been described or observed following long-term therapy with nomifensine. An immune etiology has been proven for hemolysis, and one is suspected for other side effects.[169]

The record simply does not support Dr. Temple's suggestion that the antibody findings would have been assessed in a context divorced from evidence of Merital's allergy-inducing potential. Thus, Dr. Richard D. deShazo, M.D., Professor of Medicine and Pediatrics and a member of the Section of Clinical Immunology and Allergy, Tulane University Medical Center, stated in an August 8, 1986, letter to the subcommittee.

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[164] See Neftel, et al., "Durch Cyanidanol-3 (Catergen) induzierte immunhamolytische Anamie." *Schweiz.med.Wschr.*, vol. 110, no. 10 (1980). See also, Neftel, et al., "(+)-Cyanidanol-3 Induced Immune Haemolytic Anaemia" in the *International Workshop on (+)-Cyanidanol-3 in Diseases of the Liver*, ed. Conn, 1981, The Royal Society of Medicine, London.

In September 1985, Catergen, like Merital a few months later, was withdrawn from the worldwide market because of reports of fatal hemolytic anemia associated with its use. The Italian Health Office removed Catergen from the market after receiving three such reports from the Naples area. This action led other regulatory agencies to follow suit, resulting in a worldwide market withdrawal by the drug's sponsor. See the September 6, 1985, letter to German physicians from the drug's sponsor, in subcommittee files.

[165] See Brattig, et al., "(+)-Cyanidanol-3 Induced Fever and Its Pathogenesis," in *International Workshop on (+)-Cyanidanol-3 in Diseases of the Liver*, supra, pp. 228-233.

[166] See Neftel, et al. "(+)-Cyanidanol-3 Induced Immune Haemolytic Anaemia," in *International Workshop on (+)-Cyanidanol-3 in Diseases of the Liver*, ed. Conn, 1981, the Royal Society of Medicine, London.

[167] Dr. Neftel advised the subcommittee in an August 12, 1986, letter that a "particular reason to include nomifensin in the ongoing studies [for drug-specific antibodies] was the observation that the side effect pattern of nomifensin is in part similar to that of (+)-Cyanidanol-3 (Catergen) . . ." In subcommittee files.

[168] His September 30, 1986, letter to the subcommittee is in subcommittee files.

[169] Hearing, page 98.

> It is my opinion that it was important that the regulatory agencies reviewing Merital know that the drug was highly immunogenic. . . . This is especially the case in view of the fact that the drug was . . . associated with hypersensitivity reactions.[170]

The antibody findings for Merital strongly suggested allergy a the likely basis for many already observed adverse reactions tha appeared to be of immunological origin. In fact, FDA's recommen dation in late 1985 to relabel Merital to highlight the immun pathogenesis thought to underlie the various adverse reactions a sociated with the drug's use was based, in part, on data that eve tually came to its attention showing antibodies forming again Merital and/or its metabolites. In a November 5, 1986, letter to th subcommittee, FDA cited an article by Drs. Mueller-Eckhardt an Salama in the August 22, 1985, *New England Journal of Medicin* which reported the detection of such antibodies in the blood Merital patients who developed hemolytic anemia as providi "support for the conclusion that an immunopathogenetic mech nism might explain other adverse events linked to nomifensi (i.e., lupus, nephritis, etc.)."[171] FDA cited this article as amo those few that "were important to the division's conclusion that 'immune mediated risk' was deserving of emphasis in Merital's beling."[172]

As will be described later in this report, the sponsor failed report to FDA several serious and sometimes fatal reactions Merital of a possibly allergic nature. The significance of data Merital's immunogenicity would have been enhanced had these actions been reported.[173]

Dr. Adkinson testified that the very high rate of antibody form tion reported to be induced by Merital administration constitute "very strong clue" that an immunological mechanism or mec nisms linked many of the combinations of adverse reactions th were reported for Merital and were listed in the drug's original beling.[174] Dr. Adkinson found that Merital's "significant immu genic potential" suggested a "common immunologic origin" many of the disorders associated with the drug's use.[175]

The record reveals that only once in the six years FDA spent viewing the Merital NDA did any agency reviewer recognize t an unusual syndrome may have been associated with the use

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[170] His August 8, 1986, letter to the subcommittee is in subcommittee files.

[171] Hearing, page 480.

[172] Ibid.

[173] In this connection, the following exchange between the subcommittee chairman an Adkinson occurred: "Mr. Weiss: Our investigation has revealed that prior to the approv Merital, substantially more serious Merital associated immune reactions occurred than known at that time to FDA. In your judgment, would not a large number of serious im reactions raise significant safety concerns for a drug known to have a very high rate of ant formation? Dr. Adkinson: Yes. In my judgment, it should have at least indicated a serious for concern." Hearing, page 5.

[174] Hearing, page 8. In a similar vein, Dr. Richard deShazo, an immunology and a expert from Tulane University Medical Center advised the subcommittee:

> The high frequency of drug-specific antibody reported to be induced by Merital coul in my opinion, reflect a common immunologic origin for many of the hypersensitivit reactions reported for the drug.

His August 8, 1986, letter to the subcommittee is in subcommittee files.

[175] Hearing, page 7.

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Merital. In a memorandum of a November 9, 1983, telephone conversation with Dr. John Griffin of the United Kingdom's Committee on Safety of Medicines, Dr. Paul Leber wrote:

> I inquired on an informal basis whether or not a syndrome characterized by fever and/or hemolytic anemia and/or liver injury had been identified in England. . . . [Dr. Griffin] thought this syndrome of abnormal fevers was associated with liver changes and said the English interest in the syndrome had been piqued by the possibility that it was linked to the recognized syndrome of neurological damage and systemic injury seen with Zimelidine [an antidepressant never approved for use in the United States that was withdrawn from the worldwide market in 1983 because of large numbers of hypersensitivity reactions associated with its use].[176]

In his testimony, Dr. Leber conceded that pre-approval knowledge of Merital's immunogenicity "would have forced us to consider new issues." [177] Had FDA known that Merital induced drug-specific antibodies in a large percentage of persons exposed to it, the agency might have pursued the question of whether a syndrome of "fever and/or hemolytic anemia and/or liver injury" was associated with its use. As it was, Dr. Thomas Hayes, FDA's supervisory medical officer for Merital, in a June 26–July 2, 1984, review regarding Merital, noted for reasons unrelated to the drug's potential immune toxicity, that zimelidine was associated with a "hypersensitivity" syndrome involving "fever, myalgia and/or arthralgia, headache, [and] liver dysfunction, . . . often combined with nausea, later called a flu syndrome." [178] At no time in this or any other review, however, did he make any connection between this syndrome and the similar pattern of reactions that had been frequently reported, in varying combinations, for Merital.

During his appearance before the subcommittee, Dr. Leber testified that the

> . . . question in 1984 when we made the approval was whether or not we had enough information to reach a conclusion about a linkage between a variety of syndromes and then stress this hypothesis in nomifensine's labeling. Dr. Adkinson, who obviously thinks that we did, has the advantage of retrospect.[179]

Dr. Adkinson's "advantage of retrospect" in part reflects his awareness of data on Merital's extraordinary antibody-inducing capacity that were available well before FDA approved Merital in 1984. One of the "heralds" of Merital's "predisposition" to induce allergic reactions, Dr. Adkinson has noted, was "the fact that Merital stimulated drug-specific antibody in almost everyone who received it." [180] Had FDA been aware of Merital's immunogenicity

[176] Hearing, page 498.
[177] Hearing, page 18.
[178] Hearing, page 187.
[179] Hearing, page 17.
[180] See Dr. Adkinson's September 29, 1986, letter to the subcommittee, Hearing, pages 528–529.

before it approved the drug, it would have been far better situated to appreciate that several types of adverse reactions reported for Merital merely represented various manifestations of the drug's toxicity to the immune system. As Dr. Adkinson, reflecting on the Merital experience, concluded:

> In this case drug developers and regulators remain skeptical that "knowing that antibodies are formed doesn't tell you what happens (to people)." This attitude results in an increased monitoring threshold such that it requires dozens of cases of hemolytic anemia, hyperpyrexia and vasculitis syndromes to bring the seriousness of the problem to the attention of those concerned. Because immunologic drug reactions manifest themselves in a variety of different ways and inflict damage on many different organ systems, it is especially important to know that the drug has allergic potential so that adverse experiences with the drug can be interpreted appropriately.[181]

2. FDA DID NOT ENSURE RECEIPT AND REVIEW OF IMPORTANT INFORMATION PERTINENT TO ITS ASSESSMENT OF THE SAFETY OF MERITAL

A. FDA's Regulation of Merital Did Not Reflect Review of Important Articles in the World Literature Relevant to the Drug Safety

Dr. Paul Leber, Director, FDA's Division of Neuropharmacological Drug Products, testified that, had he known that Merital was associated with a very high degree of antibody formation, "I think I would have explored the issue." [182] As stated earlier, FDA was not aware of a December 1983 paper in the Swiss literature reporting Merital to be highly immunogenic until the subcommittee's May 22, 1986, hearing.

In a November 5, 1986, letter to the subcommittee, FDA cited two letters and one paper published in the world literature in *19*[illegible] as "important to the division's conclusion that an 'immune mediated risk' was deserving of emphasis in Merital's labeling" in November 1985.[183] *A review of relevant publications in the world literature suggested the drug's toxicity to the immune system well before 1985.*

Dr. Adkinson testified that as early as July 1979, an antibody drug reaction was postulated as the cause of serious adverse reactions to Merital in the medical literature.[184] From this point on numerous publications appeared in the world literature documenting the clinically diverse manifestations of Merital's apparent toxicity to the human immune system. FDA's regulation of the drug does not reflect consideration of these publications.

One publication cited by FDA as important to its decision in late 1985 to recommend that Merital be re-labeled to emphasize its apparent immune toxicity was a paper appearing in the August [illegible], 1985, *New England Journal of Medicine* on Merital-associated [illegible]

[181] Ibid.
[182] Hearing, page 19.
[183] Hearing, page 480.
[184] Hearing, page 5. He referred to F. Bournerias, B. Habibi, "Nomifensine-Induced Immune Haemolytic Anemia and Impaired Renal Function," *The Lancet*, July 14, 1979, pages 95–6.

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molytic anemia that reported the detection of antibodies against the drug and/or its metabolites.[185] However, the frequency and heterogeneity of Merital-associated antibody response, as earlier discussed, was documented almost two years earlier in the December 3, 1983, *Swiss Medical Weekly*.

Another publication cited by FDA as important to its decision in late 1985 to recommend that Merital's labeling highlight its wide-ranging allergic potential was a letter published on June 8, 1985, in *The Lancet* concerning five cases of "allegedly allergic fever and alveolitis." [186] Dr. Adkinson testified, however, that an allergic basis for Merital-associated fever and alveolitis (inflammation of the small airsacs of the lung) was posited as early as 1980 in the Swiss literature.[187] Moreover, it is noteworthy that the authors of the 1985 *Lancet* letter cited nine references in the medical literature from 1979-1983 in support of the observation that

> [r]eported side-effects [for nomifensine] include drug fever, hepatic reactions, haemolytic anaemia, and a lupus-like syndrome. These side-effects have usually been assumed to be allergic rather than toxic in nature.[188]

Other publications in the world literature, reporting on additional cases of Merital-associated *fever*, postulated that they represented allergic responses to the drug. For example, a *1980* paper in the Dutch literature, describing two such cases, concluded:

> The eosinophilia, ... and the quick appearance of the changes after repeated administration of nomifensine, speaks more for an *allergic* than for a direct hepatotoxic reaction. . . . [189](*Emphasis supplied.*)

In addition, three papers published by Scandinavian authors in *1981* called attention to the probable allergic basis for Merital-associated fever. One of these, which reported on two fever cases, one of which also involved liver injury, concluded: "The mechanism is most likely based on an allergic basis, because the reaction took place after a time span, was dose independent and immediate after the provocation dose of nomifensine." [190] In stating that this "hypothesis is supported by the observation of a case of nomifensine-induced immune hemolytic anemia [Bournerias et al., 1979]," the authors emphasized the potentially common immunological basis for drug-associated fever and hemolytic anemia. The authors also contributed to a second paper, this one featuring one fever case, which similarly concluded:

[185] Hearing, page 480.
[186] See FDA's November 5, 1986, letter to the subcommittee, Hearing, page 479.
[187] Hearing, page 6. See Hunziker, et al., "Arzneifieber auf das Antidepressivum Nomifensin (Alival)," *Schweizerische Medizinische Wochenschrift*, September 6, 1980, Vol. 11, No. 36, pages 1295-1300.
[188] See Hamm, et al., "Alveolitis Associated with Nomifensine," *The Lancet*, June 8, 1985, pages 1328-9.
[189] Dankbaar, Mudde, *Ned. Tijdschr.Geneesk*, 124, No. 51, 2184-86.
[190] Nielsen, Lund, "Drug Fever Due to Nomifensine Treatment in Patients with Endogenous Depression," *Int. Pharmacopsychiat.*, 1981. The authors concluded their paper with a recommendation:

> ... to stop nomifensine treatment when inexplicable fever appears during treatment. A provocation test has to be done under strict observation in a hospital because of the risk of allergic shock.

> It is possible that allergy disposes to the development of this complication to the treatment. . . . The occurrence of immune haemolytic anemia by 1 patient points in the same direction.[191]

The third article, reporting two cases of fever that recurred upo rechallenge, emphasized the probability that they represented "a immunological reaction against [the] preparation." [192] Both pa tients had slightly abnormal liver parameters and eosinophil which resolved upon discontinuation of the drug.

Dr. Adkinson testified that a *1980* paper on Merital-associate fever included a case in which fever was accompanied by granul matous hepatitis,[193] a toxic manifestation of a possible allergic hypersensitivity reaction to the drug. Two other papers publishe in *1981* reported similar liver findings. One in the Scandinavian li erature reported on the drug's association with hepatic epithelio cell granulomas that resolved after the drug was discontinued.[19 The other, published in the Swiss literature, described three Me tal patients found with eosinophilic granulocytes in their liver Lymphocyte transformation tests, used to ascertain whether a dru has immune toxic potential, were positive for two of the patient and one patient also experienced a spiked temperature short after taking the drug. The paper concluded that the clinical cours the presence of eosinophilic granulocytes, and the results of ly phocyte transformation tests all "speak for a drug-induced allerg event.[195]

Another paper published in *1980* postulated that a case of Me tal-associated liver injury (i.e., jaundice) represented a "hypersen tivity" reaction to the drug.[196] Similarly, in reporting a severe ca of Merital-associated hepatitis, a *1984* paper in the British lite ture concluded:

> The four week interval between the start of treatment and the appearance of jaundice, blood and tissue eosinophilia,[197] and hepatitis similar to viral hepatitis but with no demonstrable viral infection or autoimmune disease suggested a drug induced hypersensitivity reaction.[198]

A Merital patient who developed thrombocytopenia or a pressed blood platelet count was featured in another *1984* report the British literature. The authors offered a "drug induc immune mechanism" as the probable explanation for this adver reaction.[199]

[191] Nielsen, Lund, Ebert-Petersen, and Liisberg, "Drug Fever During Nomifensine Tr ment," *Ugeskrift for Laeger*, May 18, 1981.
[192] Weihe, Thybo, and Magnussen, *Ugeskrift for Laeger*, May 18, 1981.
[193] Hearing, page 6.
[194] Thomsen F., Jensen, H.C., Thomsen P., "Liver involvement after nomifensine." *Ug Laeger* 1981, Vol. 143, page 1331.
[195] Marti, et al., "Granulomatose Hepatitis nach Gabe des Antidepressivums Nomife (Alival)," *Schweizerische Medizinische Wochenschrift*, Vol. 111, December 12, 1981, page 1
[196] Brandes, et al. "Gelbsucht nach Nomifensin," *Die Medizinische Welt*, October 31, 1 1607-8.
[197] The patient experienced a 35 percent eosinophil count, which resolved upon discont ation of the drug.
[198] Vaz, et al., "Hepatitis induced by nomifensine," *British Medical Journal*, November 1984.
[199] See Green S., Naorose-Abibi, SMH, "Nomifensine and thrombocytopenia," *British Med Journal*, March 17, 1984, Vol. 288, page 830.

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The third publication FDA cited in its November 5, 1986, letter to the subcommittee as important to its decision in late 1985 to recommend that Merital be relabeled to emphasize the "immune mediated risk" associated with its use was a paper published in the July 27, 1985, issue of *The Lancet* on Merital-associated immune vasculitis.[200] Citing several literature publications predating FDA's approval of Merital on December 31, 1984, this paper opened with the following statement.

> Immune-toxic reactions to nomifensine often occur within 4 weeks of the start of therapy, presenting as high fever and an influenza-like syndrome (myalgia, arthralgia, malaise), sometimes followed by various organ manifestations such as hepatotoxicity (including granulomatous hepatitis), haemolytic anaemia, thrombocytopenia, alveolitis, or interstitial pneumonia.[201]

A Merital-associated lupus-like syndrome, which is essentially a generalized vasculitis,[202] was reported in a letter published in *1983*.[203] In reporting two cases of immune vasculitis, the authors of the July 27, 1985, *Lancet* paper cited this article in stating that "[n]omifensine can cause immune-allergic adverse reactions, including a lupus-like syndrome." [204]

Thus, prior to 1985, the medical literature reveals ample evidence of various ways in which Merital had proven toxic to the immune system. FDA's pre-market regulation of the safety of Merital did not include consideration of this evidence.

The committee believes it is essential that FDA, in weighing the risks of a new drug against its purported benefits, make every effort to obtain and review all publications in the world literature relevant to an intelligent and responsible assessment of the safety and efficacy of such a drug, particularly a new chemical entity that the agency is considering for general release for the first time to physicians and the consuming public.

Dr. Paul Leber testified that, because the "world literature . . . is voluminous," FDA could not be expected to have been aware of the December 3, 1983, Swiss paper on Merital's antibody-inducing properties.[205] However, an English abstract of that article was included in an annotated bibliography for "nomifensine" obtained by the subcommittee staff from the Medical Literature Analysis and Retrieval System (MEDLARS) maintained by the National Library of Medicine.

The titles and very frequently the abstracts of articles published in tens of thousands of journals in the world literature are entered into MEDLARS. Articles appearing in foreign language publications are generally listed with English titles and, in many cases, are accompanied by English abstracts.

[200] Hearing, page 479.
[201] P. S. Schoenhoefer and J. Groeticke, "Fatal Necrotising Vasculitis Associated with Nomifensine," *The Lancet*, July 27, 1985, page 221.
[202] Thus, Dr. Temple referred to the two vasculitis cases reported in the July 27, 1985, *Lancet* as "arguable cases of rapidly progressing lupus." Hearing, page 21.
[203] Garcia-Morteo and Maldonado-Cocco, "Lupus-like syndrome during treatment with nomifensine," *Arthritis Rheum* 1983; 28: 936.
[204] Schoenhoefer, supra.
[205] Hearing, page 18.

Of the several publications concerning Merital's allergic pote tial that were discussed above, five appear in the MEDLARS bit ography on nomifensine with English abstracts and six others a peared with their titles, including English titles for articles writt in foreign language publications.

FDA's library has computer access to MEDLARS. The agen however, does not require its reviewers to obtain and exami titles and, where available, English abstracts accessed from t system for potentially relevant articles in the world literature c cerning new drugs under their review.[206]

Defending the absence of such a requirement, FDA has advi the subcommittee that "neither the reviewers nor the library h sufficient time or resources for routine searches not directed at s cific questions . . ." [207] The committee notes that the subcomm tee staff reviewed all the MEDLARS listings for "nomifensine" less than two hours. The committee believes that only minimal sources are required to scan virtually the entire world literatu for articles that may be relevant to the safety and efficacy of a n drug under review. The computer printouts generated from MI LARS enumerating the pertinent world literature in very c densed form supply valuable information on a drug that multi periodic submissions by sponsors over the long period of an I and NDA review do not provide. FDA should institute procedu to ensure that its reviewers avail themselves of the agency's acc to this important computer technology.

In 1985, FDA revoked Section 310.9 of its regulations, which empted sponsors from submitting to FDA copies of relevant pu cations in the literature if they appeared in journals received the agency that were included on the FDA's "designated journ list.[208] This section apparently relieved Hoechst of the legal obl tion to submit to FDA reprints of several publications in the w literature, including foreign language publications, concerning safety of Merital. The committee believes that FDA should take steps to ensure that sponsors submit to it in a timely prominent manner *copies* of all publications in the literature may be pertinent to its evaluation of the safety and efficacy new drug under review, including *translations* of all such publ tions appearing in foreign languages.

FDA's decisions can only be as good as the information u which they are based. The Merital experience dramatizes FI unfortunate lack of awareness of years of published world exp ence with the drug. FDA must remedy this unacceptable situat

[206] See FDA's November 5, 1986, letter to the subcommittee, Hearing, page 490.
[207] Ibid.
[208] Hearing, page 171.

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B. FDA Does Not Require the Submission of Labeling, "Dear Doctor" Letters, and Other Important Regulatory Information Related to the Foreign Marketing of New Drugs Under Review in the United States

Foreign Labeling

In November 1985, almost one year *after* approval, FDA recommended that Hoechst relabel Merital to emphasize the immune toxicity that the agency thought might link several reported drug-associated adverse effects. Well *before* approval, however, the drug's West German labeling warned physicians about "immunologically caused" side effects associated with the drug's use. In *February 1984* the German labeling for the drug stated:

> In rare cases, the following *hypersensitivity reactions* have been observed: Skin reactions, changes in liver function tests, drug fever (occasionally over 40°C), symptoms as with a cold (pulmonary infiltration), yellow discoloration of the skin and darkening of the urine (hemolytic anemia). In these cases [Merital] is to be discontinued immediately and the treating physician is to be informed that, because these *immunologically caused* reactions do, of course, disappear, nevertheless they do make medical countermeasures necessary (Letter translated from the German and emphasis supplied.) [209]

By contrast, Hoechst made no attempt to highlight the immunological basis of these reactions in the labeling proposed to and approved by FDA. Nor did the original U.S. labeling warn of the need immediately to discontinue the drug even at the first sign of a relatively benign immunological reaction such as fever.[210] Furthermore, reactions such as fever and liver alterations that were characterized as "hypersensitivity reactions" in the drug's February 1984 German labeling were not listed among those presumably regarded as manifestations of "immune mediated injury" listed in the drug's U.S. labeling that was revised in November 1985.

Dr. Peter S. Schoenhoefer, formerly head of the drug safety department of the West German Federal Health Office, advised the subcommittee that the German label warning concerning Merital's immune toxicity was made when Hoechst's application for a license for the drug was approved in 1983.[211] "At that point in time," Dr. Schoenhoefer explained, "there was published evidence in the German medical literature showing the immunogenic properties of the drug." [212] This evidence, Dr. Schoenhoefer wrote, "led the Federal Health Office to demand from Hoechst the inclusion of these adverse reactions in the data sheet." [213]

[209] See the subcommittee's July 14, 1986, letter to FDA, Hearing, page 444.

[210] Not until November 13, 1985, in fact, did Hoechst advise FDA that it was modifying the Merital labeling to state that the drug "should be discontinued in patients developing any degree of fever." See the November 13, 1985, letter from Mr. Dennis Bucceri, Vice President, Regulatory Affairs, Hoechst's U.S. affiliate, to Dr. Paul Leber, in subcommittee files.

[211] See his November 19, 1986, letter to the subcommittee, which is in subcommittee files.

[212] Ibid. Dr. Schoenhoefer specifically cited Sill, et al., "Durch chemische Noxen verursachte Alveolitiden," *Atemse-Lungenkrkh. Jahrgang* 8, Nr. 6, 1982, pages 331-335, which concluded, on the basis of three case reports involving Merital, that the drug should be added to the list of chemical substances known to cause immune-allergic alveolitis.

[213] See his November 19, 1986, letter to the subcommittee, which is in subcommittee files.

As earlier discussed, FDA's discovery in mid-1984 that Merital was associated with fevers in excess of 40°C or 104°F led the agency to reconsider whether and under what conditions Merital could be approved as a safe antidepressant. Yet, according to a chronology published by the West German Ministry of Health, the drug's German labeling was revised on October 16, 1980, to warn that fevers above 40°C had occasionally been observed.[214]

FDA did not receive a copy of any German labeling for Merital prior to approving the drug.[215] The agency has advised the subcommittee that it does not require sponsors to submit to it all labeling for a new drug approved in other nations that is either under investigation or has been approved for marketing in the United States.[216] The committee believes that such a requirement could provide valuable additional information on the manner in which foreign regulatory authorities as well as sponsors view a new drug under review in the United States. As FDA acknowledged, "such documents could provide clues to the existence of unrecognized hazards or might, when a sophisticated regulatory agency demands significant changes in labeling or marketing status, alert us to the need for more information.[217] Now, as a result of the subcommittee's investigation, FDA has stated that it will consider "whether we should modify regulations and/or guidelines to request certain information of this sort." [218]

Foreign "Dear Doctor" Letters

In February 1985, several months before Merital's market launch in the United States, the Arznei-telegramm, a German medical journal, published a warning concerning various clinical manifestations of an immune-allergic reaction associated with the use of Merital, including fever; serum sickness-like complaints with muscle aches; joint pain and flu symptoms; thrombocytopenia; liver injury including granulomatous hepatitis; and bronchopneumonia.

Although no similar warning appeared in the labeling accompanying the drug when it was launched in July 1985, Hoechst responded to alleged charges from the Arznei-telegramm that it had suppressed information concerning the "influenza-like syndrome and other hypersensitivity reactions associated with use of the drug in a "Dear Doctor" letter sent to German physicians in February 1985. According to Hoechst's letter, the Arznei-telegramm had maintained:

> . . . that as the manufacturer . . . of nomifensine Hoechst itself had not informed physicians about the properties of its own products. The Arznei-telegramm is referring to an *influenza-like syndrome* and other such undersirable side effects which after our experiences with zimelidine make this kind of instruction necessary.[219] This as-

[214] Dated Novermber 18, 1986, that chronology is in subcommittee files.

[215] See, for example, FDA's November 5, 1986, letter to the subcommittee, Hearing, pages and 475.

[216] Hearing, pages 476-7.

[217] See FDA's November 5, 1986, letter to the subcommittee, Hearing, page 477.

[218] Ibid.

[219] In a December 17, 1986, letter to the subcommittee, Dr. Peter S. Schoenhoefer, who is filiated with the Arznei-telegramm, wrote: "In February 1985, we were convinced that Hoec

Contin

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sertion—that we had not informed physicians sufficiently concerning the properties—namely, the side effects—of nomifensine is false. All of our documentation—that is, the instructions for patients and professionals, the Remedia Hoechst, scientific monographs and also our advertising—have contained indications *since the beginning of 1984* of just these rare side effects that the Arznei-telegramm has accused us of suppressing. In the instructions for use we described the hypersensitivity reactions following ingestion of nomifensine. . . .[220] (Emphasis supplied.)

FDA did not receive a copy of this "Dear Doctor" letter,[221] nor, for that matter, is there any evidence that it received a copy of the Arznei-telegramm, that was published that same month. The subcommittee's investigation revealed, in fact, that FDA does not require sponsors to submit to it "Dear Doctor" letters distributed to practitioners in other nations concerning new drugs under investigation or approved for marketing the United States.[222] Had it done so, FDA might have learned that the sponsor was emphasizing to German physicians' aspects of Merital's toxicity that were not described in the package inserts made available to American physicians when the drug was approved by FDA, or when the drug's market campaign was launched in the United States.

There is also no indication in the record that, prior to the withdrawal of Merital from the market in January 1986, FDA received "Dear Doctor" letters sent to German and U.K. physicians on September 24 and 30, 1985, respectively. The letters warned of serious Merital-associated hypersensitivity reactions, including three fatal cases of immune hemolytic anemia, two fatal cases of immune vasculitis, a fatal case of acute liver dystrophy, and a case of lupus.[223] The U.K. letter stated that revised labeling was under discussion with U.K. regulatory authorities in which "more emphasis will be given to hypersensitivity reactions." [224]

had more information on the immune-allergic nature of the side-affects of nomifensine and the range of diseases caused by the drug . . . I published my warnings in the Arznei-telegramm, indicating that Hoechst had more data than they were willing to communicate." In subcommittee files. While the drug's West German labeling listed several "immunologically caused" hypersensitivity reactions associated with its use, Dr. Schoenhoefer stated that it "never clearly described" the "pathogenic links between the initial influenza-like syndrome and hepatitis, insterstitial pneumonia or hemolytic anemia." Ibid. of nomifensine and the range of diseases caused by the drug . . . I published my warnings in the Arznei-telegramm, indicating that Hoechst had more data than they were willing to communicate." In subcommittee files. While the drug's West German labeling listed several "immunologically caused" hypersensitivity reactions associated with its use, Dr. Schoenhoefer stated that it "never clearly described" the "pathogenic links between the initial influenza-like syndrome and hepatitis, insterstitial pneumonia or hemolytic anemia." Ibid.

[220] See the subcommittee's July 14, 1986, letter to FDA, Hearing, page 444.

[221] See FDA's November 5, 1986, letter to the subcommittee, Hearing, pages 471 and 476.

[222] Hearing, page 476.

[223] In subcommittee files.

[224] On December 18, 1985, Hoechst sent another "Dear Doctor" letter to U.K. physicians, which accompanied new labeling for the drug, which was not forwarded to FDA until January 1986, after the drug had been withdrawn from the market. It was sent at FDA's request in late January 1986.

The "Dear Doctor" letter called attention to new labeling on "hypersensitivity reactions," which emphasized that "Merital should be discontinued immediately after the onset of the first signs of a [hypersensitivity] reaction and not used again in any circumstances." In subcommittee files.

Foreign Regulatory Developments

FDA did not learn until January 1986 that as of September 198 Hoechst had stopped promoting the drug in the United Kingdom In a January 27, 1986, memorandum, Dr. Leber wrote that on Jan uary 13, 1986, he was given the January 8, 1986, issue of *SCRIP*, British trade publication, that:

> . . . suggested that the CSM (i.e., the English drug regulatory authority) might be on the verge of taking some sort of action against the product. Furthermore, it indicated that Hoechst UK had issued a Dear Doctor letter about Merital and had allegedly ceased promotion of the product in the U.K.[225]

Dr. Temple testified that "[w]e had not known of these develo ments, but we did know that Merital was still being actively pr moted in the United States." [226]

Until it received the *SCRIP* article in January 1986, FDA had i inkling of the serious questions being raised by U.K. regulatory a thorities concerning the continued approvability of Merital. Ce tainly, no such questions were being entertained by FDA. Once t trade publication came to Dr. Leber's attention, however, he co tacted the sponsor and the Committee on Safety of Medicines f information on the status of the drug in the U.K. One week lat Hoechst notified FDA that the drug was being withdrawn from t market worldwide. The sponsor emphasized safety problems e countered in the U.K. as critical to its decision.[227]

In a January 27, 1986, memorandum, Dr. Leber wrote:

> Certainly, it seems clear that we would all have been better off knowing sooner, and in full detail, what other national regulatory agencies were doing and why. Perhaps the whys and wherefores of their actions are most important.[228]

As FDA stated in its November 5, 1986, letter to the subcomn tee:

> Notice of the pending British action and associated Dear Doctor letters, provided more than a year after our approval action, and changes in promotion, on the other hand, are very much the sort of information we would like as soon as possible and, in the present case, were based on new information that we would also have liked to see promptly.[229]

FDA does not require sponsors to inform it of important reg tory developments concerning new drugs marketed outside United States that are under investigation or have been appro

[225] In subcommittee files.

[226] Hearing, page 14.

[227] Hoechst's January 23, 1986, product withdrawal letter states: "We have been inform an increase in the number of reports of serious hypersensitivity reactions, notably hem anemia, occurring in nomifensine-treated patients in the United Kingdom." In subcomr files.

[228] In subcommittee files.

[229] Hearing, page 477.

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for marketing in this country.[230] The committee believes that such a requirement would enable FDA to keep abreast of events that can provide vital insights into the recent track record of new drugs being marketed abroad.

Evaluations Obtained from Foreign Regulatory Authorities

A *May 1981* evaluation by Australia's Department of Health concluded:

> Nomifensine can cause an allergic or idiosyncratic reaction consisting of one or more of the following:
> (a) drug fever,
> (b) functional and morphological disturbance of liver function,
> (c) eosinophilia,
> (d) on occasions a picture suggestive of interstitial pneumonitis.[231]

By this early date, Australia's Department of Health was already speculating whether some of these possibly immunologic signs and symptoms comprised a syndrome associated with use of the drug. The evaluation further stated: "Whether fever, eosinophilia and liver damage form part of a syndrome and how frequently such a syndrome can occur in a complete or incomplete form are at present matters for speculation but of some concern." [232]

Hoechst Australia received this evaluation in *August 1983*, and forwarded it that same month to Dr. A. John Nelson of Hoechst's U.S. affiliate. However, FDA did not learn of this evaluation until the subcommittee brought it to the agency's attention on July 14, 1986.[233]

Similarly, there is no evidence that FDA learned that Hoechst withdrew its marketing application for Merital in Sweden on May 14, 1984, following a report from the Swedish regulatory authority indicating that "the therapeutic value of nomifensine was inferior to that of already existing drugs of the same category" and that the "incidence of fever and liver reactions was unacceptably high." [234] Swedish regulators had also concluded that "hemolytic anemia . . . belong[ed] to the same kind of adverse effects as fever and liver reactions." [235] All three were considered part of a drug-induced immune syndrome.[236]

FDA does not currently require sponsors to submit evaluative material obtained from foreign regulatory bodies regarding new drugs under review in the United States.[237]

[230] See FDA's November 5, 1986, letter to the subcommittee, Hearing, pages 476-7.
[231] See the subcommittee's July 14, 1986, letter to FDA, Hearing, page 445.
[232] Ibid.
[233] See FDA's November 5, 1986, response to the subcommittee's July 14, 1986, letter, Hearing, pages 472 and 475.
[234] See the December 4, 1986, letter to the subcommittee from the Department of Drugs, National Board of Health and Welfare, Sweden, in subcommittee files.
[235] Ibid.
[236] Ibid. Also see the subcommittee's October 10, 1986, letter to the Swedish regulatory authority, in subcommittee files.
[237] See FDA's November 5, 1986, response to the subcommittee's July 14, 1986, letter, Hearing, pages 476-7.

The committee believes such a requirement could prove invaluable in enabling FDA to review how potentially important aspects of a new drug under its review are perceived and handled by other regulators.

3. HOECHST DID NOT MAKE TIMELY AND COMPLETE REPORTS TO FDA IMPORTANT INFORMATION PERTINENT TO THE SAFETY OF MERITAL

A. Hoechst Did Not Report Serious Adverse Reactions Associa With the Use of Merital Prior to the Drug's Approval

At the time of the subcommittee's hearing, FDA regulations quired sponsors to "promptly" report to the agency "any findi associated with a new drug under investigation "that may sugg significant hazards, contraindications, side effects, and precauti pertinent to the safety of the drug." [238] Based on an examinat of submissions made to FDA by Hoechst *after* approval of Meri *the subcommittee's investigation has revealed that the comp failed to report to FDA at least 30 drug-associated deaths know it prior to that approval.* Many of these deaths were suggestive possible allergic reactions to the drug. *In addition, Hoechst w held from FDA important information in its possession regard some reports of Merital-associated deaths it did make to FDA p to approval.*

By *1979*, for example, Hoechst was notified of a July 14, 1 Merital-associated death from *hemolytic anemia* of a 76-year Swiss woman suffering from chronic lympathic leukemia.[239] senior physician in her case was Dr. K. Laemmel. When Hoe was notified of the case cannot be determined from the records rently available to the subcommittee. However, at a February 1979, meeting at Hoechst AG, Dr. Zapf, a Hoechst AG official, ported, that in light of the Laemmel case in Luzern and the le which Hoechst Roussel (HRPI), U.S.A., will submit to the FDA other reported cases of drug-associated hemolytic anemia], he n contact the BGA [the West German Federal Health Office]." [24 *least one official of Hoechst's U.S. affiliate appears to have kn of this fatal case at that time.* In attendance at the February 1979, meeting was a "Dr. Nelson." [241] Dr. A. John Nelson, forr

[238] 21 CFR § 312.1(a)(6). On March 19, 1987, FDA replaced this subsection with § 312.32 IND regulations, that requires sponsors to report to FDA within 10 working days any " pected" adverse experience that is "serious"; that is, that suggests a "significant hazard c indication, side effect or precaution." 52 Fed.Reg. 8797, 8837.
[239] The patient received 25 mg. of Merital twice daily beginning on May 8, 1978. On M 1978, she was hospitalized for fatigue, vertigo, and suspected "bleeding anemia." Direct and rect Coombs tests were positive at this time. Her anemia was assessed as autoimmune her ic. She later attempted suicide at home by taking 12 tablets of an unknown medication. On 26, 1978, she re-started Merital at 300 mg/day. On July 12, 1978, she experienced nausea, ing, vertigo, and developed jaundice. She was transferred to the medical clinic due to recu fainting and jaundice and died on July 14, 1978. The clinic physician assessed the cause of as follows:

> This is obviously a hemolytic attack in the case of a known chronic lymphatic leuk mia. In our ward Hb was 4.5, whereas it had been 11.6 g two days earlier. Also clinica ly there were signs of an acute severe anemia; in addition to this, the jaundice appear to be increasing. . . The patient probably died of hypoxia [oxygen deficiency] due anemia.

That she had developed leukemia obviously complicated the assessment of Merital's role death.
[240] The memorandum of this meeting by Dr. S. M. Streichenwein of Hoechst AG is in su mittee files.
[241] Ibid.

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ly Senior Vice President and Medical Director of Hoechst-Roussel Pharmaceuticals, Inc., also worked for the company's U.S. affiliate at that time. This case was not reported to FDA until August 19, 1986, more than seven years after Hoechst learned of it and seven months after the drug was withdrawn from the market worldwide.[242] In its August 19, 1986, submission to FDA, Hoechst maintained that the case was reported as a "death" in one of the tables included in an international safety update sent to the agency on January 9, 1984. Nothing in the simple designation of a "death" captures the detailed information available to Hoechst concerning the case that had originally led the company to number it among those it suspected as involving Merital-induced hemolytic anemia.

Another death reported to the company in *1980* involved *Coombs-positive hemolytic anemia* (the destruction of red blood cells), symptoms of anaphylactic shock, and icterus (i.e., jaundice).[243] On June 19, 1986, Hoechst submitted a "15-day alert" report to FDA that described the death in mid-1980 of a female Merital patient in Florence, Italy. Included in the submission was a memorandum by Ap. E. Woelfel of Hoechst AG of a February 19, 1981, conference with a Dr. Sesso of Hoechst's Italian affiliate. The memorandum stated that the patient discontinued use of Merital after seven months on the drug. Several months later, she took one 25 mg. capsule and developed general malaise, after which she discontinued the drug for two days. On the third day, she took another 25 mg. capsule and eventually collapsed

> . . . with symptoms of anaphylactic shock; *hemolysis* and icterus were also diagnosed. *The Coombs test was positive.* Then the patient was treated in various departments of a large hospital, where, despite all therapeutic efforts, she died.[244] (Emphasis supplied).

Ms. Woelfel's February 1981 memorandum was circulated to at least two other Hoechst AG officials.[245]

Hoechst AG, as well as the company's Italian affiliate, actually learned of this case in 1980. According to a January 28, 1981, letter from Hoechst's Italian subsidiary, Dr. Pola of Hoechst AG wrote a Dr. Carandente about the case on December 15, 1980, and at some unspecified time, discussed the case in Frankfurt with a Dr. Invernizzi. Dr. Pola's December 15, 1980, letter was not included in Hoechst's June 19, 1986, submission to FDA.[246]

That the 1980 Italian death also may have involved anaphylaxis constitutes additional evidence that the patient experienced an allergic or hypersensitivity reaction to Merital.[247] Interestingly, Dr. Temple testified on May 22, 1986, that "we don't think we had" any reports of Merital-associated anaphylaxis.[248]

[242] Hoechst's August 19, 1986, submission to FDA is in subcommittee files.

[243] See the subcommittee's July 7, 1986, letter to FDA, Hearing, pages 439-442. Hoechst's June 19, 1986, submission to FDA described this case as involving "[s]ymptoms of anaphylactic shock; hemolysis; icterus." Ibid.

[244] In subcommittee files.

[245] Ibid. These two officials were Drs. Zapf and Taeuber.

[246] Ibid. The precise data on which Hoechst AG or its Italian affiliate initially learned of the case was not supplied to FDA.

[247] In fact, Dr. Robert Temple cited "anaphylaxis" as among the "kinds of [drug] reactions [that] are more commonly perceived as hypersensitivity reactions." Hearing, page 20.

[248] Hearing, page 20.

Hoechst advised FDA on June 19, 1986, that this case was one several classified in a table included in a January 9, 1984, subm sion to FDA as either an "unspecified reaction" or an "ill defin experience."[249] Until June 19, 1986, however, no mention w made of the nature of the adverse experience or, for that matt that it resulted in death.

It is difficult to imagine that cases of fatal hemolytic anemia not receive close attention by Hoechst officials in 1979 and 19 since, by that time, the company was sufficiently concerned ab the few reports it had received in 1978 and 1979 of non-fatal he lytic anemia that it had initiated the European Surveillance P gram—an ambitious program featuring immunological investi tions in three European countries—"in order to determine the s ousness of the problem."[250]

Notwithstanding reports received by Hoechst of fatal, drug-a ciated hemolytic anemia, Dr. A. John Nelson of Hoechst's U.S. filiate, who may have learned of at least one such case by Febru 1979,[251] stated at the December 3, 1981, meeting of the Psyc pharmacology Drugs Advisory Committee (PDAC) that "[t]he sa of the drug is not in doubt."[252] Thus, the focus of this meet like that of the two subsequent PDAC meetings on Merital, was the drug's efficacy, not its safety.

By *early 1984*, Hoechst was informed of another Merital-assoc ed death involving *hemolytic anemia*—this time of a 57-year French woman. The patient, who had recovered from an episod Merital-induced hemolytic anemia and renal failure in 1982, to capsules, or 125 mg., of the drug in February 1984.[253] Within half hour she developed hemolysis and Quincke's edema and hospitalized with chills and jaundice. She died on February 1984, thirteen hours after she was admitted to the hosp Hoechst knew about this death at least by February 1984, denced by the date of a letter to the company's French affiliate cussing it.[254] Although Hoechst apprised FDA of this death July 28, 1986, it did not submit details on the case until Augus 1986.[255] The case had previously been reported to FDA on No

[249] According to Hoechst's June 19, 1986, submission to FDA, a September 19, 1983, from Hoechst AG simply referred to this case as a "zwischenfall" (incident). In subcom files.

[250] See the January 1980 report of Dr. Suzanne Streichenwein of Hoechst AG on the E an Surveillance Program that was included in the sponsor's July 7, 1980, amendment Merital NDA.

[251] As earlier stated, Dr. Nelson may have attended a February 22, 1979, meeting at H AG at which the 1978 death from hemolytic anemia of a Merital patient in Luzerne, S land, was discussed.

[252] See pages 61-2 of the verbatim transcript of this meeting, which is in subcommitte

[253] Hoechst reported that she attempted suicide when she took this dose. Interestingly, er, 125 mg. is not significantly greater than the 100 mg. daily dosage recommended in th labeling for Merital. Furthermore, patients who took substantially more of the drug su For example, the report of hemolytic anemia and renal failure reported in the Novem 1980, *British Medical Journal* involved a patient who took 2 grams or 80 capsules of th and recovered. See Prescott, et al., "Acute haemolysis and renal failure after nomifensir dosage," *British Medical Journal*, Vol. 281, pages 1392-3. This case was among the origir reports of hemolytic anemia that HRPI submitted to FDA on March 13, 1979. That an o age was involved in this case obviously did not deter the sponsor from reporting it as r relevant to Merital's capacity to induce immune hemolytic anemia.

[254] This letter was dated February 23, 1984. See Hearing, page 314. Hoechst's French a was aware of the patient's initial hemolytic anemia episode at least by February 10, 19 date it wrote a letter on the case.

[255] The description of the case derives from the details contained in this submission, v in subcommittee files.

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ber 1, 1985, as involving "hemolytic anemia" with an "unreported" outcome.

On August 19, 1986, seven months after Merital was withdrawn from the market, Hoechst notified FDA of another pre-approval death of a Merital patient who had developed *hemolytic anemia.* In this case, however, this 79-year-old French patient was reported to have died of another cause well after she had recovered from Merital-associated hemolytic anemia.[256]

Dr. Temple testified during the subcommittee's May 22, 1986, hearing that, when it approved Merital, FDA had received *no* reports of fatal, drug-associated hemolytic anemia.[257]

The importance FDA eventually attached to fatal reports of Merital-associated immune hemolytic anemia cannot be underestimated. In its post-approval consideration of Merital's safety, reports of such fatalities were of paramount concern to FDA. As Dr. Temple testified:

> I don't know the specific numbers [of hemolytic anemia reactions] that they [Hoechst] cited as being the basis for their withdrawal . . . But, more important to us in all this was the fact that fatalities began to appear . . . What impressed us was that people were dying of it. That seemed very important.[258]

In fact, Dr. Leber testified before the subcommittee that initial reports of fatal Merital-associated hemolytic anemia prompted a major revision in mid-1985 in the drug's labeling:

> You have to understand that we were interested, during the Spring and Summer of 1985, in having the labeling state in a very forthright way that fatal hemolytic anemias could have occurred in association with nomifensine treatment. . . . We wanted, at that point, to emphasize that hemolytic anemia was a much bigger risk than it had seemed earlier, because the fact that you develop a hemolytic anemia is not, in and of itself, too important if most of the cases were benign. . . . But prior to that there was really no appreciation of the seriousness of it because there hadn't been fatal cases.[259]

The committee believes that Hoechst was responsible for and legally required to make prompt, complete, and accurate reports to FDA of all significant Merital-associated adverse reactions known to it or any of its foreign affiliates. The committee can only speculate on the significance that FDA would have attached, prior to approving Merital, to several reports of death involving hemolytic anemia that it did not receive until *months after Merital was removed from the market.* However, in light of the drug's post-approval regulatory history, the committee concludes that, at th very least, Hoechst's failure to report to FDA these fatalities ass ciated with use of the drug rendered Merital, as originally labele misbranded within the meaning of § 502(a) of the Food, Drug, an Cosmetic Act.

[256] The patient received Merital from November 7, 1980 to May 20, 1983. On April 1, 1983, during a hospitalization, she developed hematoma of the right pectoralis major muscle requiring drainage under local anesthesia. A positive direct Coombs test raised the possibility of hemolysis. In June 1983, her clinical status was noted to be good and in November 1983, it was evaluated as "normal." Subsequently, however, the patient died of "another cause." Records on the case were enclosed in a November 30, 1984, letter from Dr. Claude Spriet-Pourra of Hoechst's French affiliate.

[257] Hearing, page 12.

[258] Hearing, pages 40-1.

[259] Hearing, pages 31-2.

On June 13, 1986, the subcommittee informed FDA of a numb of other Merital-associated deaths that may have involved allerg reactions to the drug that were known to Hoechst prior to t drug's U.S. approval but were not reported to FDA until *after* a proval.[260] For example, Hoechst learned at least by March 2 1982,[261] of a Welsh case involving a 91-year-old woman who di on March 5, 1982, in association with an "allergic skin reactio and "allergic pneumonitis [acute inflammation of the lung]."[2] The sponsor, however, waited more than 3 years, until October 3 1985, to report the case to FDA as a 15-day alert report.[263]

The sponsor was also notified by January 31, 1983,[264] of t death on January 13, 1983, of a 62-year-old French woman who e perienced fever and other adverse effects suggestive of a possil allergic reaction to the drug.[265] Hoechst initially mentioned t report to FDA in an April 24, 1986, submission,[266] two years months later. Dr. Robert Temple's testimony before the subcomm tee that "at the time of approval, in six years of marketing [of M ital outside the United States] . . . people had not died of [Merit

[260] This letter and all of the details on these cases which follow, appear in Hearing, p 431-8.

[261] The earliest record in FDA's files indicating Hoechst's knowledge of the case was the that a Hoechst UK official signed an adverse reaction report concerning the case, which March 23, 1982.

[262] According to a March 1982 adverse reaction report, on February 25, 1982, three days nomifensine administration, a 91-year-old female "developed an extensive erythematous *all skin reaction.*" [Emphasis supplied.] On February 28, 1982, secondary bronchial pneumoni veloped, and the patient was diagnosed as having "*allergic pneumonitis.*" [Emphasis supp The patient also had a "spiking temperature" that day. By March 1, 1982, the "skin cond had deteriorated to the extent that the total skin area was covered in erythematous lesions third of the skin had sloughed off and bleeding was noted from all mucous membranes. March 2, 1982, the patient's *eosinophil* count was a marketedly elevated *22* percent. The pa was also obviously *anemic*—her hemoglobin had descended to 11.6 g/dl, down from 13.6 g/ December 24, 1981, and 13.4 g/dl on January 14, 1982. The cause of death was cited as bro pneumonia; all lung areas were consolidated and the bronchi were filled with white green

The case report itself states that the patient's skin and lung conditions had been diagnos "allergic" reactions to Merital. In addition, eosinophilia, fever, and anemia (particularly *lytic* anemia) have all been associated with hypersensitivity reactions to the drug.

[263] In its October 31, 1985, submission, the sponsor included this case among those "previ reported to FDA on or before May 7, 1984, but are now known to involve deaths." The sul mittee staff could not locate any report of this case made on or before May 7, 1984. In any all of the details reported on October 31, 1985, were known to the sponsor well before M 1984.

[264] Hearing, page 300.

[265] The patient was given Merital for a year. On January 4, 1983, she developed *hyperpy* her temperature had risen to 40° C or 104° F. Additionally, the patient experienced shock, nea, and loss of consciousness. On January 5, 1983, the patient first showed liver functio abnormalities; her LDH had risen to 610, markedly higher than the upper range of nor 330. On January 8, 1983, the patient had pneumonopathy of the left side. On January 9 a 1983, further evidence of liver function test abnormalities was found, with SGOT, SPT, and LDH markedly in excess of normal.

According to Hoechst's May 15, 1986, submission, the original suspicion of "maligna perthermia has not been confirmed." Although Dr. Claude Spriet-Pourra of Hoechst's affiliate wrote that "possible septicemia is the final diagnosis," the sponsor acknowledge hemocultures, which are often relied upon to diagnose septicemia, "were negative." Wh report lacks sufficient detail definitively to conclude that the patient experienced an reaction to Merital, many of her symptoms—including hyperpyrexia, pneumonopathy function abnormalities, shock, dyspnea, and loss of consciousness—have all been associate hypersensitivity reactions to the drug.

[266] The first mention of the case was in an April 24, 1986, quarterly report to the NDA. Records on the cases, however, were not submitted to FDA until May 15, 1986.

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associated] fever"[267] may reflect the firm's failure to report this case prior to the drug's U.S. approval.

The nomifensine-associated death on November 30, 1977, of a 62-year-old German man from thrombocytopenia purpura was reported to Hoechst in a December 2, 1977, letter.[268] Hoechst reported this case to FDA as a 15-day alert report on May 15, 1986,[269] 8½ years later.[270] Another thrombocytopenia-related death, this one involving a Belgian user who also suffered a cerebral hemorrhage, was known to Hoechst at least by September 17, 1982,[271] and *was known by Hoechst's U.S. affiliate by June 13, 1984, prior to FDA approval.*[272] It was not reported to FDA, however, until May 15, 1986.

By December 21, 1981, Hoechst's French affiliate had learned of the death of a 72-year-old female Merital patient.[273] Viral hepatitis, leukopenia, thrombocytopenia, thrombin increase, and abnormal liver function tests were implicated in her death.[274] The death was first mentioned to FDA in a July 30, 1986, submission, with additional details provided to the agency on August 15, 1986.[275] Hoechst claimed that the case had been reported in a table included in a January 9, 1984, submission to FDA as "liver damage" or "hepatitis" or "worsening of viral hepatitis." No other details, including the fact of the patient's death, were supplied at that time.

Hoechst had known since January 1984[276] of the *anemia-related* death of a 59-year-old female Merital user who died on October 10, 1983, but waited until October 31, 1985, to inform FDA in a 15-day alert report that she had developed anemia, and to provide the agency with records it had received on the case in January and February 1984.[277] Whether the patient had developed *hemolytic*

[267] Hearing, page 16.

[268] The patient's psychiatrist discussed the case in a December 2, 1977, letter to Hoechst AG. This patient had been taking Merital for approximately two weeks prior to the onset of the reaction. According to his psychiatrist, the patient was treated for "our idea of an existing *allergic* diathesis [i.e., condition]." The patient appeared to be anemic in that his hemoglobin was recorded as 10.9 g/dl. It is noteworthy that an immune hemolytic anemia death reported by Hoechst to FDA on May 21, 1985, also involved thrombocytopenia [i.e., a depressed platelet count of 53,000/mm³]. An immune hemolytic anemia case reported in the *British Medical Journal* (Prescott, et al, 281: 1392, November 22, 1980) also involved thrombocytopenia [i.e., a depressed platelet count of 46,000/mm³].

It is noteworthy that "a drug induced immune mechanism" has been offered as the probable explanation for some cases of Merital-associated thrombocytopenia. See, for example, the case reported by Green, et al., in the *British Medical Journal*, 288: 830, March 17, 1984.

[269] The sponsor stated in its May 15, 1986, submission, that this case had been reported to FDA on January 9, 1984. The only reference to a thrombocytopenia purpura case in the January 9, 1984, submission was contained in one of several tables appended to the submission. The January 9, 1984, submission mentioned no details of the case, including the fact of the patient's death, although the sponsor had received them several years before.

[270] Hearing, page 42.

[271] Hearing, page 288.

[272] See the inspectional observations (FDA Form 483) issued by FDA field investigators to Hoechst's U.S. affiliate in March 1987, in subcommittee files.

[273] Hearing, page 304.

[274] The patient reportedly discontinued use of the drug in March 1981, some months before her death, and Hoechst AG believes that it was unrelated to use of the drug.

[275] The facts recited here come from these submissions, which are in subcommittee files.

[276] Hoechst UK was contacted by the coroner's office about the case on January 12, 1984. According to a February 2, 1984, letter from Hoechst UK, a January 19, 1984, inquest into the patient's death was attended by an official from Hoechst UK and one from Hoechst AG.

[277] On October 31, 1985, Hoechst advised FDA that she developed "cardiac arrhythmia and shock in the face of severe anemia." One line of a computer printout submitted to FDA on May 7, 1984, listed the case as follows: "cardiac arrhythmia—asystole—death." No mention was made at that time that she had also developed "severe anemia," although that fact was prominently mentioned in records received by the firm in January and February 1984.

anemia cannot be discerned from the report.[278] The patient course, however, which culminated in a shock-like reaction, is n inconsistent with some Merital-associated reports of fatal hemolyt anemia submitted to FDA following the drug's approval.[279]

Dr. Robert Temple testified that FDA was particularly "i pressed" by reports of Merital-associated "fatalities" that includ cases of "arguably . . . allergic type responses" to the drug.[2 Hoechst's failure to report to FDA deaths brought to its attenti from 1977-1984 that may fall into this category prevented FI from appreciating before it approved Merital that the drug m have been capable of inducing fatal allergic reactions.

The subcommittee's June 13, 1986, letter to FDA also cited sev al other Merital-associated deaths known to Hoechst prior to FI approval of the drug that were not reported to FDA until after th approval, including three deaths involving cardiac compli tions,[281] and ten cases of drug-associated suicide and/or fatal ov dose.[282] On July 30, 1986, subsequent to the subcommittee's lett Hoechst also reported a pre-approval Merital-associated death volving hyponatremia (i.e., salt depletion).[283]

In addition, on January 30, 1987, Hoechst reported to FDA se German deaths associated with the use of Psyton, a combinat product containing Merital, that were known to the comp before Merital's U.S. approval.[284] Included among those dea were five suicides and two cases of lung edema.

Despite a number of potentially important deaths involving molytic anemia, allergic pneumonitis and exfoliative dermat

[278] There is no indication that a test for hemolysis was performed.

[279] On September 16, 1983, the patient received the drug for the first time. She die hours after taking her last tablet. The patient became severely anemic, with her hemo descending to 7.5 g/dl. Records indicated no previous history of anemia. Air passages in h piratory system contained flakes of mucoid secretions. Cut lung surfaces showed some mil gestion in the right lung in the apical region. Focal chronic bronchitis was also noted. T tient reportedly had difficulty breathing.

According to the coroner's report of January 23, 1984, a reviewing pathologist "said th thought that a therapeutic dosage of Merital when the deceased was in an anaemic con caused the side effects and led to death."

Evidence that the patient died from cardiac arrhythmia was apparently lacking, as D zanne M. Streichenwein of Hoechst AG noted in a memorandum of a January 19, 1984, m in the United Kingdom. Moreover, that the terminal event may have involved cardiac con tions does not necessarily deny the contributory role of the patient's anemia. In this conn the death of a UK woman attributed to hemolytic anemia that Hoechst reported to FDA o 21 and September 11, 1985, ultimately involved ventricular fibrillation progressing to as

[280] Hearing, page 40.

[281] A report of a fatal case involving congestive heart failure was received by Hoechst C on October 3, 1983, but was not reported to FDA until May 15, 1986. A second fatal cas entailed worsening of a pre-existing atrial flutter condition that occurred in France in 19 also reported to FDA on May 15, 1986. Another pre-approval death, this one involving a defined cardiac reaction" was reported to FDA on October 31, 1985.

[282] Four of these cases were reported to FDA on October 31, 1985, while six others w ported to FDA on May 15, 1986. As some of the submissions on these deaths indicate, s ports raise questions, not only about Merital's efficacy as an antidepressant for some p but also whether the drug increases the risk of suicide in some patients. For example, a n gist reportedly told a Hoechst official on October 20, 1978, that Merital might have "trig one of the suicides reported to FDA on May 15, 1986. In subcommittee files. Similarly, ac to a Hoechst AG memorandum dated June 16, 1981, the physician who reported anothe tal-associated suicide "wishes to know whether there has been any report lately indicati [Merital] drives depressed patients to suicide." In subcommittee files.

[283] This July 30, 1986, submission is in subcommittee files. Hoechst claimed that this case was reported in a table appearing in its January 9, 1984, submission to FDA. No including the fact of the patient's death, were submitted to FDA at that time. It appea the company number assigned to the case that Hoechst was notified of the case in 1981.

[284] In subcommittee files. Psyton combined Merital and clobazam, a benzodiazepine de not marketed in the U.S. Psyton was marketed in Germany from 1982 to 1985.

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fever, thrombocytopenia, and liver damage[285] that were reported to Hoechst between 1977 and 1983, Dr. P. D. Stonier, a Hoechst UK official, stated in a paper presented on the safety of Merital at an October 1983 symposium in San Diego California, that "no deaths have been associated directly with the use of nomifensine." [286]

Hoechst also failed to report to FDA large numbers of serious, nonfatal Merital-associated immune reactions prior to the drug's approval on December 31, 1984. Close examination of a submission Hoechst made to FDA on November 1, 1985, approximately 10 months *after* approval, revealed that at least 94 cases of hemolytic anemia/hemolysis had been reported to the firm prior to the drug's approval on December 31, 1984.[287] This means that, with the addition of 14 other such cases that the company reported to FDA on April 24, 1986,[288] and January 30, 1987,[289] Hoechst had received at least 108 reports of hemolytic anemia/hemolysis prior to the drug's approval. Another analysis performed by the subcommittee staff, largely based on data the sponsor furnished the subcommittee, yielded a similar finding; [290] namely, that the firm knew of 109 cases of hemolytic anemia/hemolysis prior to the drug's approval. Experts have noted that no other drug has been associated with more than 100 documented cases of immune hemolytic anemia.[291] Hoechst, however, claimed to have reported only 41 hemolytic anemia cases to FDA prior to that approval.[292] As Dr. Charles F. Thayer of Hoechst's U.S. affiliate noted in a September 25, 1985, letter, there were sharp "discrepancies" between the numbers of hemolytic anemia cases "reported to FDA" and those contained in the files of the company's German headquarters.[293] Actually, both the subcommittee staff and FDA,[294] in preparation for the subcommittee's hearing, concluded that the sponsor had only reported between 27 and 30 such cases prior to approval, a circumstance that probably reflects the confusing, if not misleading, manner in which the sponsor purportedly reported several hemolytic anemia cases in summary tabular form to FDA in January 1984.[295]

The sponsor cited the marked increase from 1984 to 1985 in numbers of reports of hemolytic anemia cases from abroad as the principal reason for withdrawing Merital from worldwide distribution.[296] However, had Hoechst reported all hemolytic anemia reactions known to it prior to Merital's US approval, a marked increase from worldwide marketing experience with the drug would have been observable for 1984 as compared to 1983.[297] Information submitted by Hoechst to the subcommittee, as well as its November 1, 1985, and April 24, 1986, submissions to FDA, indicated that Hoechst, prior to Merital's approval, had reported 11 cases for 1983 and four cases for 1984. Had Hoechst made full reports prior to approval, a marked increase, from 19 to 51 cases, would have been discernible in those two years.[298]

Serious, Merital-Associated Adverse Reactions Reported to FDA Prior to the Drug's Approval Were Not Submitted in a Timely Manner

Dr. Temple testified that in mid-January 1986, FDA "contacted the Committee on Safety of Medicines" who expressed "concern about the increased number of cases of hemolytic anemia reported during *1984* and 1985 without clear explanation [emphasis supplied]." [299] Dr. Paul Leber, in fact, conceded that Merital, which "had been marketed for a long time in Europe with a very good safety record, . . . may have fallen apart in *1984* and 1985 . . ." [300] Nothing in the record, however, reflects any awareness by FDA prior to or shortly after approving Merital in late 1984 that the drug began to "fall apart" in Europe in 1984.[301]

The subcommittee's review of the sponsor's major safety submissions to the Mertial NDA and IND, uncovered delays—sometimes amounting to several years—in some of the reports of Merital-associated adverse effects submitted to FDA prior to the drug's approval. [302] The subcommittee asked FDA whether it regarded the delays as constituting violations of agency reporting requirements but the agency declined to respond as it was conducting an investigation of this matter.[303] The committee believes that pre-market reports of serious, even fatal Merital-associated reactions years after they came to the sponsor's attention could hardly comprise "prompt" reports of "findings" pertinent to the drug's safety within the meaning of § 312.1(a)(6) of FDA's IND regulations.

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[285] Hoechst had reported four liver-related deaths to FDA on July 22, 1981. Hearing, page 49. A fifth such death was reported to FDA on January 9, 1984. In subcommittee files.

[286] Hearing, page 49.

[287] The sponsor had advised the subcommittee staff that the first two digits of the case numbers listed in that submission represent the year in which Hoechst received the adverse reaction report. It was based on this information that the subcommittee arrived at the number of hemolytic anemia cases known to the company prior to the drug's approval on December 31, 1984. Hearing, page 35.

[288] Seven such cases were reported to FDA on April 24, 1986. Hearing, page 36.

[289] On January 30, 1987, Hoechst reported large numbers of adverse reactions associated with the use of Psyton, a combination of Merital and clobazam (a benzodiazepine derivative not marketed in the U.S.) that was marketed in Germany from 1982 to 1985. The submission contained seven additional hemolytic anemia cases known to Hoechst prior to U.S. approval of the drug.

[290] Hearing, page 36.

[291] Mueller-Eckhardt and Salama, *Dtsch.med.Wschr.* 111 (1986), page 1262.

[292] See the sponsor's November 1, 1985, submission to FDA, Hearing, page 193.

[293] Hearing, page 36. Dr. Thayer noted that, as of the date of his letter, Hoechst's U.S. affiliate had reported 45 such cases while 89 were indicated to be in the company's German files.

[294] Dr. Leber testified: "By my own count, there may be between twenty-seven and thirty. And I just discovered that the other day in preparing for this hearing." Hearing, page 35.

[295] On the misleading manner in which these cases were reported in a January 9, 1984, safety update, see Hearing, pages 460-1.

[296] Hearing, page 39.

[297] Hearing, pages 39-40.

[298] Hearing, page 41.

[299] Hearing, page 14.

[300] Hearing, page 74. In his prepared testimony, Dr. Temple stated: "It is possible, however, that the CSM itself stimulated such reporting [of increased numbers of hemolytic anemia during 1984 and 1985] by highlighting the risks of antidepressant drug use in a communication to physicians, urging that physicians be sure to report adverse reactions occurring with these drugs. The publication specifically noted the occurrence of hemolytic anemia with nomifensine, perhaps leading physicians to recognize additional cases of it." Hearing, page 14. The publication to which Dr. Temple referred is the July 1985 issue of *Current Problems*. The committee is aware of no such publication from the CSM prior to 1985 that can be cited as possibly responsible for the increased number of hemolytic anemia reports made during *1984*.

[301] In fact, the record does not reflect such an awareness until FDA's January 1986 contact with the Committee on Safety of Medicines.

[302] For example, a July 22, 1981, submission to the Merital IND on liver toxicity associated with commercial marketing of the drug outside the United States revealed that delays up to 3 years occurred in the reporting of serious adverse liver reactions to the agency. This submission also revealed lengthy delays in reporting several liver-related deaths, including, for example, one delay of 3 years, nine months. The subcommittee staff's May 1986 review was attached to the subcommittee's July 14, 1986, letter to FDA and appears at Hearing, pages 454-7.

[303] See FDA's November 5, 1986, response to a subcommittee letter of July 14, 1986. Hearing, page 483.

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Hoechst's Reports to FDA Did Not Include All Relevant Records in Its Possession

As already noted, some of Hoechst's adverse reaction reports to FDA—including reports of death—did not include important records in the firm's possession. The subcommittee's investigation uncovered additional evidence of the sponsor's failure to share with FDA detailed information it had concerning Merital-associated adverse experiences submitted to FDA prior to the drug's approval. In briefly mentioning a liver-related death associated with use of the drug in a January 9, 1984, submission,[304] for example, Hoechst neglected to include records indicating that the patient had developed urticaria and fever as well as inflammatory liver infiltrates—all of which are suggestive of a possible allergic reaction—and that one of her treating physicians had sought information on levels of Merital-specific antibodies found from the serological series done on her.[305]

In addition, Hoechst sometimes reported adverse reactions to FDA in a manner that should have indicated that it was withholding relevant information in its possession. Unfortunately, FDA overlooked or acquiesced to this. For example, FDA allowed Hoechst to "report" significant adverse reactions to the drug—most notably hemolytic anemia reactions—merely as numbers of cases listed in tables appended to a January 9, 1984, submission, without any details concerning clinical course or the characteristics and medical histories of the patients involved.[306] Similarly, FDA allowed Hoechst to "report" other potentially important adverse reactions on May 7, 1984, merely as one-line entries in a computer printout, unaccompanied by any additional information.

The committee believes that FDA should require sponsors, when reporting serious reactions associated with an investigational new drug, to supply all relevant details in their possession concerning the nature and course of such reactions, as well as the characteristics and medical histories of the patients who experience them. Absent such information, FDA cannot make responsible evaluations of the toxicity of such drugs.

B. Hoechst Did Not Comply With FDA's Adverse Reaction Reporting Requirements for Approved New Drugs

Non-Compliance With 15-Day Alert Reports

Section 314.80(c)(1) of FDA's regulations requires that serious and unexpected (i.e., "not listed in the current labeling for the drug")[307] adverse reactions associated with the use of *approv* new drugs be reported to FDA "within 15 working days of initi receipt of the information." "Initial receipt" according to FDA, i cludes the date that any foreign affiliate of a sponsor is notified such a reaction.[308] The subcommittee's review reveals that 15-d reports of serious and unexpected adverse experiences associat with use of Merital outside the United States rarely arrived FDA on time.[309] Information FDA supplied for the hearing reco confirmed this finding.[310] The agency, however, took no regulato action in connection with Hoechst's failure to meet 15-day repo ing requirements.[311]

According to § 314.80(a) of FDA's regulations, a "serious" re tion always includes a "death" and an "unexpected" reaction cludes "an event that may be symptomatically and pathophysio gically related to an event listed in the labeling, but differs fr the event because of greater severity . . ." Since fatal liver inju or the potential for such injury, was not mentioned in the Meri labeling, Dr. Temple testified that the liver-related death of female Merital user who had pre-existing liver disease that was ported to the sponsor on December 2, 1985,[312] "perhaps sho have been" submitted to FDA as a 15-day report.[313] Hoechst, h ever, waited six weeks to report the case to FDA.

Dr. Temple noted, however, that the

> . . . importance of the case to us was that it was a case of hemolytic anemia in which either the anemia itself, or more probably the treatment of the anemia ith steroids, led an already fragile patient to die. So, we count that as something that might have been the responsibility of nomifensine, possibly related to hemolytic anemia.[314]

Hoechst classified the case as a possible hemolytic anemia fat ty and did not submit it to FDA as a 15-day report, probably cause it did not regard the reaction as "unexpected" within meaning of § 314.80(a) of FDA's regulations, since by the time firm learned of the case, the Merital labeling reflected the dr association with fatal hemolytic anemia.

Section 314.80(c)(2) of FDA's regulations requires that all rep of serious adverse experiences associated with domestic market of a recently approved new drug that are not subject to the 15-alert requirement—that is, serious but expected [i.e., listed in drug's current labeling] reactions—be included in quarterly rep

[304] In this submission, Hoechst described the case as follows:

> The fifth patient [who died from liver-related disease] received nomifensine for approximately 4 days (data imprecise). A month later she had jaundice and abnormal liver function tests (peak SGOT = 1325, normal range and units not given). Four months after nomifensine treatment the patient died with severe liver damage. A postmortem biopsy (no autopsy) showed postmortem necrosis. The relationship to nomifensine is unclear and doubtful.

See the subcommittee's July 14, 1986, letter to FDA, Hearing, page 447.

[305] See the subcommittee's July 14, 1986, letter to FDA, Hearing, page 447. FDA advised the subcommittee that these records were not supplied to FDA. See FDA's November 5, 1986, letter to the subcommittee, Hearing, pages 474-5.

[306] See the subcommittee's July 14, 1986, letter to FDA, Hearing, page 448. These tables were presented in such a misleading and confusing manner that it was not even clear how many hemolytic anemia reports they purportedly showed. Hearing, pages 460-1.

[307] 21 CFR § 314.80(a)

[308] In a November 5, 1986, letter, FDA advised the subcommittee:

> We expect drug firms to adopt procedures to ensure that adverse reaction informa tion is expeditiously communicated among company officials and affiliates. Thus, th timeclock will generally be considered as running when the foreign affiliate receive the information indicating that the 15-day criteria have been met. The result of this that U.S. applicants are responsible for establishing reasonable mechanisms to ensu rapid information transfer from their foreign affiliates. Hearing, page 484.

[309] Hearing, page 42.

[310] Hearing, pages 225-338.

[311] See Testimony of Dr. Robert Temple, Hearing, page 42.

[312] The case was reported to the sponsor while the patient was still alive on October 25 Her death was reported to the company on December 2, 1985.

[313] Hearing, page 50.

[314] Hearing, page 50.

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submitted to the agency. Accordingly, Hoechst waited until it submitted its quarterly report for the last quarter of 1985 to report the case. This submission was not received by FDA until January 23, 1986,[315] after the sponsor had already withdrawn the drug from the market.

Actually, FDA was not aware of this case until long after its receipt on January 23, 1986:

> Mr. WEISS. Would we be safe in assuming that FDA was not aware of this death when it stated in a January 28, 1986, Talk Paper that "no deaths in this country known to be attributable to hypersensitivity reactions had been reported to FDA at the time of the product's announced withdrawal on January 21, 1986"?
>
> Dr. TEMPLE. Yes, I don't think we were conscious of that case.[316]

In fact, as of February 25, 1986, Dr. Thomas Laughren, then the supervisory medical officer for Merital, wrote that he was "not aware of any domestic deaths from hemolytic anemia associated with Merital use."[317]

At no time prior to Merital's withdrawal from the market did the sponsor alert FDA to this important case. That the case instead was buried, as Chairman Weiss observed, "as part of hundreds of reactions" comprising a quarterly report[318] probably contributed to FDA's lack of knowledge of it.

In view of its oft-stated concern with Merital's potential to induce fatal hemolytic reactions, FDA would likely have benefited from being promptly alerted to a report of a Merital-associated death possibly involving hemolytic anemia that occurred during the drug's brief and limited marketing in the United States. Yet, the sponsor could have plausibly argued that the report involved a case of fatal hemolytic anemia and therefore did not have to be submitted as a 15-day alert report. The committee believes that, in executing its mandate to protect the public from the toxic effects of new drugs, FDA should not exempt the report of *any* death associated with an approved new drug, regardless of the contents of the drug's approved labeling, from the 15-day alert reporting requirement.

Non-Compliance With Quarterly Report Requirements

In the preamble to its NDA re-write regulations, FDA stated that the requirement for *quarterly reports*—effective for the first three years following approval of a new drug—reflects the ". . . agency's experience that the most important safety problems with a new drug are usually discovered during the first 3 years of marketing."[319]

Hoechst included a total of 16 cases of Merital-associated adverse experiences in the reports it submitted for the first three quarters

[315] This is the date that FDA received the January 16, 1986, quarterly report that included the case.
[316] Hearing, page 51.
[317] Hearing, page 51.
[318] Hearing, page 51.
[319] See 50 Fed. Reg. 7472 (February 22, 1985).

of 1985.[320] On January 16, 1986, Hoechst submitted the fourth quarter report for 1985, which was not received at FDA until January 23, 1986, after Hoechst had announced its intent to withdraw the drug from the market. The submission contained 547 initial adverse reaction reports, 49 of which involved reactions Hoechst classified as serious, and 7 of which were designated as hemolytic anemia reactions.[321] At least 100 of the 547 reports were brought to Hoechst's attention during the third quarter of 1985. Most of these, according to Hoechst's own classification scheme, were suggestive of hypersensitivity reactions to Merital, and one was reported as a hemolytic anemia reaction.[322] By contrast, Mr. David Barash of the Reports Evaluation Branch, FDA's Division of Drug and Biologic Product Experience (DDBPE), noted that "[a]s of January 17, 1986, there are 50 domestic reports in our spontaneous reporting system . . . We have received no cases to date of hemolytic anemia."[323]

Clearly, FDA, at the time Merital was removed from the market, was not aware of the large numbers of adverse reactions in the United States that had been reported for the drug. Inasmuch as the quarterly reported contained 547 reports, Dr. Paul Leber noted in a January 27, 1986, memorandum:

> In particular, DDBPE's January 17, 1986 response to our request for a cumulative update on Merital adverse event reporting to our system contains far fewer reports (50) than were identified in the firm's January 21, 1986 submission (made in response to my January 16 inquiry). For example, DDBPE had no domestic reports of hemolytic anemia, and the firm had at least 7 in their files.[324]

The inclusion in a January 16, 1986, quarterly report to FDA many adverse reactions made known to Hoechst during the fourth quarter of 1985 accounts for much of the disparity noted by Dr. Leber. Some of that discrepancy, however, is attributable to reports that Hoechst did not forward to FDA during the previous quarter.

The committee believes that the sponsor was required to include those reports in its October 9, 1985, submission for the third quarter of 1985. As Dr. Robert Temple stated in his appearance before the subcommittee: "If they had them in time for the third quarter report, they are supposed to submit them then."[325]

C. FDA Does Not Require Sponsors To Report All Serious Adverse Reactions Associated With Foreign Use of a Drug Approved for Marketing in the United States

Dr. Temple was particularly impressed by the numbers of hemolytic anemia eventually reported for Merital. In fact, he testified that if he "had known that there were going to be fatal hemolytic anemias in significant numbers," he would not have rev

[320] Hearing, pages 42-3. Hoechst included none in its May 20, 1985, report; 4 in its 1985, report; and 12 in its October 9, 1985, report.
[321] In subcommittee files.
[322] Hearing, page 43. One U.S. hemolytic anemia reaction was reported to the sponsor tember 9, 1985.
[323] See his January 17, 1986, memorandum, which is in subcommittee files.
[324] In subcommittee files
[325] Hearing, page 43.

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his mid-1984 determination that the drug's approval be conditioned on its being restricted to second-line use.[326] Yet, reports of only four, or 50 percent, of the eight hemolytic anemia deaths currently known to have come to Hoechst's attention during 1985 were received by FDA prior to Hoechst's announcement that it was withdrawing the drug from the market.

In addition to the American hemolytic anemia death previously discussed that was received by FDA on January 23, 1985, other Merital-associated fatalities not known to FDA prior to the drug's withdrawal include:

1. A South African case reported to Hoechst AG on November 6, 1985, which was not reported to FDA until February 5, 1986;
2. A German case reported to Hoechst AG on December 9, 1985, which was not reported to FDA until February 5, 1986; and
3. A U.K. case that was mentioned in the December 16, 1985, issue of *Drug and Therapeutics Bulletin* as having been reported to the United Kingdom's Committee on Safety of Medicines, which the sponsor noted in a January 21, 1986, letter to FDA.[327]

That FDA was caught unaware in January 1986 by other nation's serious reservations about the safety, and in the case of the United Kingdom, the continued approvability of Merital, in part, may reflect its lack of knowledge of several reports of drug-associated hemolytic anemia deaths reported to Hoechst in the weeks preceding the drug's withdrawal. Prompt reporting of a South African hemolytic fatality, for example, could have shed light on the information FDA received from Hoechst on January 16, 1986, that "the South Africans were modifying the labeling of Merital to advise that it should be used only in seriously ill patients and then only with caution." [328]

Actually, however, Hoechst was not legally obligated to report any of these reactions to FDA. Because reference to fatal hemolytic anemia by this time was contained in the Merital labeling, none of these three reactions was "unexpected" within the meaning of § 314.80(a) of FDA's regulations and, therefore, was not subject to the 15-day alert requirement.[329] Furthermore, because they involved "expected" (i.e., labeled) experiences associated with use of the drug *outside the United States*, Hoechst was under no legal obligation to include them in its January 16, 1986, quarterly report, since FDA relieves from periodic reporting requirements reports of any serious, although expected (i.e., listed in the labeling), reactions occurring abroad. Section 314.80(c)(2)(iii) of FDA's regulations exempts post-marketing periodic reporting of "adverse drug experience information obtained from . . . foreign marketing experience."

[326] Hearing, page 73.

[327] Reports of these cases are in subcommittee files.

[328] Hearing, page 14. In addition a report appearing in a South African publication in April 1985 concerning a case of hemolytic anemia and jaundice leading to cardiovascular collapse concluded: "It is thus clear . . . that the use of nomifensine can be associated with a life-threatening hemolytic anemia and that the indication for its use must be made critically." See Halland, "Nomifensine-associated Hemolytic Anemia," *South African Medical Journal*, vol. 67, pages 663-4, April 27, 1985.

[329] Nonetheless, Hoechst reported the first two reactions on February 5, 1986, as 15-day alert reports.

The only way in which serious, but expected, reactions occurring outside the United States would be subject to 15-day reporting requirements would be if they met the "increased frequency" requirement set out in 21 CFR § 314.80(c)(1)(ii), which states that a sponsor "shall review periodically (at least as often as the periodic reporting cycle) the frequency of reports of adverse drug experiences that are both serious and expected, regardless of source, and report any significant increase in frequency [as defined in § 314.80(a)] as soon as possible but in any case within 15 working days of determining that a significant increase in frequency exists." However, in reviewing the frequency of reports of serious and expected adverse reactions, sponsors are not clearly required to consider deaths separately from other adverse experiences. Thus, unless the

Continued

This regulation exempts a sponsor from the post-market obligation to submit to FDA serious, even fatal, reactions reported from foreign use of a drug if the reactions happen to be listed in the drug's labeling. In the case of Merital, FDA had deprived itself by its own regulations of any legal right to timely access to information bearing on the "significant numbers" of "fatal hemolytic anemias" that were eventually of such great concern to the agency.

In reflecting on the Merital experience, Dr. Paul Leber noted in a January 27, 1986, memorandum:

> Unfortunately, if a drug does not have very much domestic marketing (or real time reporting), DDPBE will not have much data to evaluate and little basis to warn anyone about anything. This may be the case here. . . . My point is rather that if a drug is already marketed abroad, domestic reporting may not provide as good a signal as non-domestic reporting.[330]

The committee agrees and believes that FDA should amend its regulations to require sponsors to report *all* serious adverse experiences associated with foreign use of a new drug approved for marketing in the United States.

D. Hoechst Did Not Report to FDA Laboratory Study Results That Showed That Merital Was Highly Immunogenic

As stated earlier, until the subcommittee's May 22, 1986, hearing, four months after Merital was withdrawn from the market, FDA was not aware that the drug was highly immunogenic; that it induced drug-specific antibodies in a very high percentage of patients taking it. FDA's lack of awarness speaks, not only to the agency's unfamiliarity with relevant publications in the world literature, but also to the sponsor's failure to make full and timely reports of this information.

In its consideration of the initial reports it received of drug-associated hemolytic anemia, Hoechst set the stage for the significance that was to be attached to the detection of drug-specific antibodies. Merital was to be regarded as the cause of immune hemolytic anemia only in those cases where such antibodies had been detected

overall frequency of drug-associated hemolytic anemia rose, any fatal hemolytic anemia contributing to that increased frequency may not be subject to "increased fequency" 15-day reporting. Moreover, where an "increased frequency" report consists of both non-fatal and cases, nothing in § 314.80(c)(1)(ii) requires that details concerning individual cases (e.g., that involve deaths) be reported to FDA.

[330] In subcommittee files.

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Subsequent to its March 13, 1979, report of the first four cases of hemolytic anemia associated with use of Merital, Hoechst specifically disavowed the role of the drug in three cases where such antibodies had not been isolated. Hoechst classified only one of those cases—a French case—as drug-related, since only this case revealed Merital-specific antibodies in the patient's serum.[331] Hoechst, however, never reported to FDA the findings of Dr. S. H. Davis, Department of Haematology, The Royal Infirmary of Edinburgh, who in a January 22, 1980, letter to the company, wrote that he had "good evidence" of "anti-nomifensine antibody" in another of the four patients featured in Hoechst's March 13, 1979, submission.[332]

By this time, other unusual Merital-associated immunological findings had come to Hoechst's attention, none of which was reported to FDA. At a March 15, 1979, meeting at Hoechst House, London, Hoechst officials discussed the commencement of retrospective studies in France, the United Kingdom, and Germany, of blood specimens from patients taking nomifensine for at least three months to estimate "the extent and severity of the problem [of hemolytic anemia]."[333] Results from a U.K. retrospective study were reported to Hoechst officials at a July 31, 1979, meeting at Hoechst House in London. At this meeting, Dr. J. Watkins,[334] Department of Immunology, University of Sheffield, reported highly unusual immunological findings in the sera of all seven patients examined in his controlled, retrospective study.[335] None of these findings was reported to FDA.[336]

Dr. B. Habibi, a French hematologist, reported in the July 14, 1979, issue of *The Lancet* one case of Merital-associated hemolytic anémia in which drug-specific antibodies had been detected. Initially, the detection methods employed on Merital blood samples revealed no additional evidence of anti-nomifensine antibodies. Hoechst reported to FDA on July 7, 1980, that random "blood samples" taken from Merital patients who developed hemolytic anemia "have been negative for Nomifensine antibodies"[337] and immunological investigations that had been conducted of Merital-associated fever cases in Italy, Germany, and France had all yielded "negative results."[338] In a similar vein, in a 1981 article, Dr. Habibi, by then a Hoechst consultant, reported negative antibody findings in 104 serum samples that he had assayed.[339]

On July 7, 1980, Hoechst informed FDA that it had undertaken an extensive antibody investigations program called the European

[331] In a July 7, 1980, amendment to the Merital NDA, Hoechst stated: "The report [from Dr. Streichenwein of Hoechst AG] suggests that in only one of the patients thought to have had nomifensine associated hemolytic anemia were antibodies to nomifensine found [the French case]. Therefore, it is concluded that only one patient suffered from a nomifensine related hemolytic anemia." In subcommittee files.

[332] See FDA's November 5, 1986, letter to the subcommittee, Hearing, pages 473–5.

[333] The memorandum of this March 15, 1979, meeting by Dr. Suzanne M. Streichenwein of Hoechst AG is in subcommittee files.

[334] A January 10, 1979, letter from Hoechst AG to Dr. A. John Nelson of HRPI, stated that Hoechst UK had informed Dr. Watkins of the two UK hemolytic anemia cases and that Dr. Watkins had asked "to investigate the matter further." In subcommittee files.

[335] See the subcommittee's July 14, 1986, letter to FDA, Hearing, page 447.

[336] See FDA's November 5, 1986, letter to the subcommittee, Hearing, pages 474–5.

[337] In subcommittee files.

[338] In subcommittee files.

[339] Habibi, "Anti-nomifensine Antibody Causing Immune Hemolytic Anemia and Renal Failure," *Vox Sang.*, Vol. 40, 1981, pages 79–84.

Surveillance Program which was then "in progress" and was to have "continue[d] indefinitely."[340] When, however, Hoechst was advised that Dr. K. Neftel and his Swiss colleagues had developed a more sensitive detection method capable of frequently isolating drug-specific antibodies in Merital patients, the firm did not bring this matter to FDA's attention.

At a May 1982, Merital/Alival International Project Committee Meeting in Somerville, New Jersey,[341] Hoechst U.S. officials were informed by Dr. Streichenwein (Hoechst AG) that Dr. K. Neftel had recently proposed to investigate blood samples from Merital patients for the presence of drug-specific antibodies. Dr. Neftel proposed using the same method that he and his colleagues had used to detect drug-specific antibodies in patients exposed to the liver protective drug, Catergen (cyanidanol), which, like Merital, had been associated with apparent immune reactions such as fever and hemolytic anemia in Europe. Dr. Streichenwein stated that Dr. Neftel proposed to demonstrate that Merital acted as an "immune reactor."[342]

Hoechst agreed to assist Dr. Neftel in his investigations and thus began what the company later characterized as its "collaboration with Drs. Neftel and [M.] Waelti [one of Dr. Neftel's colleagues who was affiliated with the Institute for Clinical Immunology, Inselspital, Bern, Switzerland]."[343]

Correspondence between Dr. Waelti and Hoechst in early May 1982 indicates that by that time Dr. Waelti had found Merital-specific antibodies in the blood of eleven patients, including three who had developed hemolytic anemia and eight who developed fever.[344] That correspondence was not provided to FDA until October 29, 1984,[345] and, because it was buried in a submission consisting of several hundred pages, apparently escaped the notice of FDA reviewers.[346]

With the exception of the case he reported on July 14, 1979, in *The Lancet*, Dr. B. Habibi, a French consultant to Hoechst had originally found no evidence of Merital-specific antibodies in the serum samples he tested. In July 1982, he commented that the positive antibody results found by Dr. Neftel and his colleagues in blood samples that he had previously tested and regarded as negative indicated that their method "is more specific than his own technique. . .[T]his could explain why he had negative results on the same material."[347]

[340] In subcommittee files.

[341] The transcript of this meeting is in subcommittee files.

[342] See pages 159–160 of the transcript of the May 10–11, 1982, Merital/Alival International Project Meeting, which is in subcommittee files.

[343] See a July 7, 1982, letter from Hoechst AG, which was included in the sponsor's October 29, 1984, submission to FDA, in subcommittee files.

[344] Hearing, page 25.

[345] Hearing, page 25. The submission consisted of all patients who had developed hyperpyrexia in association with use of the drug. Only because one of the patients whose serum tested by Dr. Waelti for antibody had experienced hyperpyrexia was this correspondence included in the submission. In short, Hoechst was not attempting to summarize in this submission antibody findings of Dr. Neftel and his associates.

[346] Hearing, page 25.

[347] See the memorandum of a July 8, 1982, meeting between Claude Spriet Pour Hoechst's French affiliate and Dr. B. Habibi, which is in subcommittee files.

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Several Hoechst employees met with Drs. Neftel and Waelti in Frankfurt in September 1982 to discuss the latter's many positive antibody findings.[348] None of these unpublished findings was reported to FDA.[349]

More than a year after that meeting, Drs. Waelti, Neftel and three other scientists, including a Hoechst employee,[350] reported in the December 3, 1983, *Swiss Medical Weekly* their findings of Merital-specific antibodies in the blood of *51 of 51* patients given the drug.

Neither a translation of that German language article, nor a copy of it, was ever submitted to FDA. Instead, the title of the article was listed as the 94th of 97 literature references included in an annual report to the Merital IND file on December 11, 1984, more than a year after it was published and more than 2 years after Hoechst was advised of the findings it reported.[351]

Hoechst did not submit the publication, indicating that it appeared in a periodical *(Schweizerische Medizinische Wochenschrift* or *Swiss Medical Weekly)* on FDA's "designated journal list." At that time, sponsors were not required to submit copies of articles appearing on that list by virtue of Section 310.9 of FDA's regulations, which was then in effect.[352]

Dr. Robert Temple testified that if an article in the world literature "was important and if it needed to be submitted for other reasons, I would be offended at least by the idea of having it left out."[353] He was not certain, however, whether the law required the sponsor promptly to bring the findings contained in the December 1983 Swiss paper to FDA's attention.[354]

If a published paper contains important findings relevant to the safety of a new drug, the committee believes the sponsor is legally obligated to report them *promptly.* Nothing in § 312.1(a)(6) of FDA's regulations requiring prompt reporting to FDA of any "significant" finding pertinent to the safety of a new drug under investigation exempted a finding that happened to appear in a "designated journal." The legal test is not the form in which the finding is presented, but rather the significance of that finding. Moreover, Hoechst was informed of Merital's antibody-inducing properties *well over a year before they were published.*

In an October 29, 1984, submission to FDA, Hoechst included an August 23, 1984, letter from a hematological consultant, Dr. Sol Sherry, Dean of the School of Medicine at Temple University, which noted that "[a]ll patients on prolonged therapy develop IGG antibodies to the drug."[355] When confronted with this statement during the subcommittee's hearing, Dr. Robert Temple stated that "I don't think we know how Dr. Sherry knows that."[356]

[348] See the Hoechst memorandum of this meeting, Hearing, pages 153-8.
[349] Hearing, pages 24-5.
[350] Hearing, page 24. M. Perisic was listed as an employee of Hoechst Pharma AG, Zurich.
[351] Hearing, page 28.
[352] This section has since been revoked. It is noteworthy that the sponsor, in its December 11, 1984, submission to the Merital IND, did supply copies of several other papers appearing in publications that were also included on the "designated journal" list.
[353] Hearing, page 29.
[354] Ibid.
[355] Hearing, page 21
[356] Hearing, page 22

Dr. Sherry's statement likely reflects his review of the Waelti, Neftel paper, a translated copy of which he received from two Hoechst officials on July 2, 1984, six months before Merital was approved and more than five months before the paper was merely reported as one of a multitude of literature references in an annual submission to the Merital IND.[357]

Despite the evidence of Merital's antibody-inducing potential that was available to the sponsor as early as 1982, Dr. Paul Leber testified:

> It is, thus, conceivable that many people exposed to nomifensine, including those with hemolytic anemia, had the antibody, but we didn't have the laboratory facility or technology to detect it. And, so I think that also has to be factored into what was knowable at the time of approval in 1984.[358]

A laboratory method, however, was available to the sponsor *before 1984* showing that "many people exposed to nomifensine . . . had the antibody." In fact, as late as October 1985, the sponsor still considered that method valid for demonstrating the presence of anti-nomifensine antibodies.[359]

As earlier discussed, a paper by Drs. Mueller-Eckhardt and Salama in the August 22, 1985, *New England Journal of Medicine* reported the detection of drug-specific antibodies in the blood of Merital patients. As was the case with Dr. Neftel and his associates, the authors of the *New England Journal of Medicine* article were able to detect Merital-specific antibodies in blood samples that had previously been considered negative for the presence of such antibodies.[360]

The *New England Journal of Medicine* paper featured a method using the urine of persons given Merital to detect the presence of drug-specific antibodies (called an "ex vivo" method). In arguing that a method for detecting antibody was not available earlier, Dr. Leber confined his discussion to this ex vivo method:

> But I would think the record ought to state very clearly that the mechanism for detecting antibodies, nomifensine, was the subject of a major paper that Dr. Adkinson mentioned on August 22nd, 1985. . . . The point made in that paper is that in order to detect the antibody, a variety of techniques had to be used that were not generally avail-

[357] Drs. Michael F. Murphy and Charles F. Thayer of Hoechst's U.S. affiliate, incl translated copy of the paper in a July 2, 1984, submission to Dr. Sherry, which is in subc tee files.
[358] Hearing, page 19.
[359] An October 1, 1985, memorandum of a September 30, 1985, telephone conversatic Mr. Eckert, Pharmaceutical Research Radiochemistry Laboratory, by Dr. Rudiger M Hoechst AG states:

> A conversation was conducted with Mr. Eckert in order to review the ad hoc deter nation possibilities for Nomifensine antibodies available to us. . . . It can be immedi ly established: radioimmunoassay for the detection of antibodies directly exist against Nomifensine. This assay exists and is available . . . [P]lease have the publ tion of Waelti and Neftel sent to Mr. Eckert.

In subcommittee files.
[360] The authors state on page 473 of their article: "Contrary to previous reports . . . v hemolytic activity in eight serum samples studied extensively." Hearing, page 95.

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able or in broad use prior to that. . . . So, as a consequence, we have a problem of detection.[361]

The decision of Drs. Mueller-Eckhardt and Salama to use an "ex vivo" method to investigate for anti-nomifensine antibodies, however, was made years before the *New England Journal of Medicine* paper was published. In November 1984, they co-authored a paper in the *British Journal of Haematology* which reported on their use of an "ex vivo" method "to demonstrate presumptive metabolite-specific antibodies . . . against nomifensine" in a patient who developed immune hemolytic anemia.[362] The paper stated that it was *received* for publication on January 5, 1984. In fact, one of the authors advised the subcommittee staff that the detection method featured in the paper was used for the first time in October 1983.[363]

The work using the particular ex vivo method described in the *New England Journal of Medicine* article was begun in June 1984.[364] One of the authors advised the subcommittee staff that initial progress reports on their work were given to Hoechst in 1984.[365] In fact, findings for five of these 19 patients were published in the German publication, *Blut*, in September 1984.[366] Furthermore, by January 1985, Hoechst had been informed of the results concerning all the blood samples it had supplied the authors for their work.[367] In fact, their manuscript was originally submitted for publication to the *New England Journal of Medicine* on January 23, 1985.[368] One of the authors advised the subcommittee staff that the firm received a complete list of all their results by June 1985. The subcommittee, in fact, obtained a July 30, 1985, memorandum by Dr. Streichenwein (Hoechst AG) indicating that three weeks before the *New England Journal of Medicine* article was published, the company was aware of the authors' antibody test results for a total of *43* hemolytic anemia patients who had received Merital.[369] Neither this memorandum, nor the findings it contained, were submitted to FDA.[370]

[361] Hearing, page 19.

[362] See Salama, Mueller-Eckhardt, Kissel, Pralle and Seeger, "Ex vivo antigen preparation for the serological detection of drug-dependent antibodies in immune haemolytic anaemias," Vol. 58, pages 525-531.

[363] The memorandum of his May 2 and 5, 1986, telephone conversations with the subcommittee staff is in subcommittee files.

[364] See the memorandum of the subcommittee staff of its May 2 and 5, 1986, telephone conversations with one of the authors, which is in subcommittee files.

[365] Hearing, page 31.

[366] The publication was an abstract of a paper presented at the Congress of the Austrian and German Societies of Hematology and Oncology entitled "The Heterogeneity of Nomifensine-Induced Red Blood Cell Antibodies: The Use of ex vivo Antigens for Their Detection." Hoechst reported this summary in a July 12, 1985, quarterly report to the Merital NDA. So, Hoechst was obviously aware of it before the drug was first widely marketed in the United States in late July 1985. Hearing, page 30.

[367] Hoechst provided 11 of the 19 blood samples analyzed by the authors of the *New England Journal of Medicine* article. Hearing, page 30.

[368] See the memorandum by the subcommittee staff of its May 2 and 5, 1986, telephone conversations with one of the authors. He told staff that the manuscript was prepared in November and December 1984.

[369] Hearing, page 31. The memorandum stated that of the 43 serum samples tested by Dr. Mueller-Eckhardt's laboratory, 30 revealed antibodies against the drug and/or its metabolites, 6 revealed autoantibodies or suspected autoantibodies, 3 revealed questionable drug-specific antibodies, and 1 showed a reaction with FTE. Only 1 result was totally negative, while 1 other sample of whole blood could not be tested. Results from 1 other serum sample were not available.

Drs. Mueller-Eckhardt and Salama also indicated that Dr. Habibi, a French consultant to Hoechst, had confirmed the findings reported for one of the blood samples discussed in their *New England Journal of Medicine* paper.[371] Dr. Habibi apparently did additional work confirming their findings, which culminated in a report dated July 9, 1985.[372] However, the sponsor never submitted this report to FDA.[373]

With the exception of the *Blut* summary, buried in a July 1985 quarterly report, Hoechst did not report to FDA any of the findings of Drs. Mueller-Eckhardt and Salama until they were published in the *New England Journal of Medicine* on August 22, 1985. Accordingly, not until it reported that article on August 25, 1985, several weeks after the drug's marketing was launched in the United States, did Hoechst suggest modifications to the Merital labeling to reflect receipt of this information. Hoechst changed the statement in the labeling's hemolytic anemia section that antibodies against nomifensine had been "isolated" in a "few instances" to "[a]ntibodies to nomifensine and/or its metabolites have been isolated."[374] In addition to mentioning the detection of antibodies against the drug's metabolites,[375] Hoechst, as Chairman Weiss noted "dropped the implication that . . . it occurred in only rare few cases and went to a more generalized statement which, at least, did not suggest the opposite of what was the case."[376] Inasmuch as Hoechst originally emphasized the relatively few cases of drug-associated hemolytic anemia in which drug-specific antibodies were found as evidence that the reaction was not Merital-induced this change was significant.

Dr. Temple testified, however, that, in the context of hemolytic anemia, the labeling "expressed what was known to us"[377] in that

> . . . antibodies to nomifensine had only been isolated in a few of those cases at that time. In some cases, they had been looked for and not found. But, there is always the question of whether they had been looked for well.[378]

Not only had the *New England Journal of Medicine* finding been known to Hoechst well before their publication on August 2

[371] Citing a personal communication with Dr. Habibi, the authors wrote that "upon the change of serum samples with us, Dr. Habibi has been able to confirm the exclusive reactivity serum from patient 3 with Metabolite 3 but not with nomifensine." See page 473 of their pa which appears in Hearing, page 95. Assuming that this personal communication occurred p to the date the manuscript was submitted, Dr. Habibi had begun confirming their results p to January 23, 1985, the date the manuscript was submitted.

[372] A Hoechst memorandum of a September 9, 1985, visit to Dr. Habibi in Paris stated: ' Habibi is not surprised by the heterogeneity of the antibodies [reported in the paper publis in the August 22, 1985, *New England Journal of Medicine* on antibodies to nomifensine an its metabolites] which does not differ from his own results (this report dated July 9, 1985)." the subcommittee's July 14, 1986, letter to FDA, Hearing, page 446.

[373] See FDA's November 5, 1986, letter to the subcommittee, Hearing, pages 473 and 475.

[374] Hearing, page 29.

[375] Hearing, page 30. One of the problems besetting the field of antibody detection is many antibodies only respond in the presence of a drug's metabolites. In this connection, se July 14, 1986, letter to the subcommittee from Dr. Richard D. deShazo, Professor of Med and Pediatrics, and a member of the Section of Clinical Immunology and Allergy, Tulane versity Medical Center.

[376] Hearing, page 30. As Dr. Adkinson observed in his testimony, the statement that specific antibodies had been "isolated in a few cases" implied that "it was not a common fi but an exceptional finding." Hearing, page 8.

[377] Hearing, page 23.

[378] Hearing, page 22.

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1985, but the seven patients who developed hemolytic anemia whose sera were tested for the December 3, 1983, *Swiss Medical Weekly* paper on Merital's immunogenicity all were found to have developed antibodies to the drug and/or its metabolites. In short, information on frequent drug-specific antibody formation was published more than 1½ years before Hoechst proposed a labeling change concerning the detection of antibodies to the drug and/or its metabolites.[379] Once the "question of whether [anti-nomifensine antibodies] had been looked for well" was answered by use of the detection method featured in this paper, the detection of drug-specific antibodies in the blood of hemolytic anemia patients could no longer be fairly characterized as an uncommon event.

Hoechst also neglected to mention in Merital's labeling what it had known since 1982—that antibodies had been found in the blood of large numbers of Merital patients who did not develop hemolytic anemia or, for that matter, any adverse reactions to the drug. In fact, Hoechst waited until October 29, 1984, to provide FDA any reference to a finding of drug-specific antibodies in Merital patients other than some who developed hemolytic anemia.[380] This information consisted of a few pieces of correspondence buried in a massive submission on Merital-associated fever, the introduction to which concluded that "[f]ever associated with Merital administration, regardless of its magnitude, has a characteristic pattern observed with other drugs consistent with an immunologic reaction mediated by drug-induced antibodies."[381] There is, however, no evidence that any FDA reviewer considered the implications of this statement or noted correspondence supporting it that was inserted numerous pages later in that submission.

Dr. Temple testified that "I would certainly say that if I had known that antibodies were formed in everybody, I would put that in the labeling."[382] Nonetheless, he did not believe that the failure of Merital's original labeling to state this rendered the drug misbranded within the meaning of the Food, Drug, and Cosmetic Act.[383]

It is at least arguable that physicians considering whether to prescribe Merital should have known that it had been very frequently associated with drug-specific antibody formation. Once, however, the sponsor made the decision to mention such antibodies in the labeling, the committee believes the sponsor had a responsibility to assure that its discussion of them was not misleading. In this connection, the committee concludes that it was misleading (1) to single out hemolytic anemia victims who developed drug-specific antibodies without mentioning that a large number of other Merital patients also developed such antibodies and (2) to intimate that a finding of Merital-specific antibodies was a "rare" occurrence. Accordingly, the committee finds additional grounds for concluding that the drug was misbranded within the meaning of § 502 of the Food, Drug, and Cosmetic Act.

[379] Hearing, page 31.
[380] Hearing, page 25.
[381] This statement was contained in a September 25, 1984, report that was included in the October 29, 1984, submission.
[382] Hearing, page 23.
[383] Hearing, page 23.

E. Hoechst Did Not Alert FDA to the Common Immunological Origin of Many Merital-Associated Adverse Effects

On October 29, 1984, Hoechst acknowledged that, collectively, hemolytic anemia, fever, liver function test abnormalities, and eosinophilia "probably reflect different target organ sensitivities to a single immunological event." As earlier discussed, Merital's original labeling did not call attention to the drug's capacity to induce a range of apparently allergic adverse effects, some of which appear to comprise a drug-related syndrome or syndromes. And while FDA failed to note clinical evidence of the drug's allergenicity, the committee finds that, with the exception of its one-sentence acknowledgment concerning the "single immunological event" buried in a massive submission on Merital-associated fever, Hoechst did not advise FDA of the drug's wide-ranging allergic potential.

Even before the Merital NDA was submitted on December 26 1978, Hoechst apparently suspected that different types of adverse effects reported for Merital represented various manifestations o an immunological response to the drug. Thus, in a January 10 1979, letter to Dr. A. John Nelson of Hoechst U.S., a Hoechst AC official stated that, in light of the 39 reports of "hyperpyretic [i.e. high fever] reactions to nomifensine" received by the firm by De cember 31, 1978, "it was not too much of a surprise to get notice o a case observed in France" of drug-associated hemolytic anemia.[38

On March 6, 1979, Hoechst AG officials reported four cases c drug-associated hemolytic anemia to the Institute for Drugs i West Germany. That letter stated that those cases ". . . evidentl have an immunological basis" and that the company had undertal en "investigations regarding the question whether Nomifensin therapy is associated with immunological side effects."[385]

Similarly, in an October 3, 1979, letter to Dr. Sesso of Hoechst Italian affiliate, Drs. Pola and Woelfel of Hoechst AG stated tha the serum of an Italian patient had been assayed for antibodies b cause " . . . [w]e had several reports about fever under [Merita therapy . . . We are trying to explain this; the next step is t assume some immunopathological course (drug fever in the liter ture)."[386]

Professor A.L. de Weck, Director, Institute for Clinical Immunc ogy, Inselspital, Bern, Switzerland, and a co-author of the Decer ber 3, 1983, Swiss report on Merital's immunogenicity, noted in September 30, 1986, letter to the subcommittee that "immunolo cal side effects of Nomifensine were recognized (and partly pu lished by us) as early as 1981. . . ." These "side effects," he conti ued, "were certainly known to the company who introduced t drug and to the control authorities."[387]

When positive antibody findings did emerge from the work Drs. Neftel and Waelti, the firm was clearly aware of the probab ty that certain reported adverse reactions were immunological character. Thus, for example, Hoechst received a May 10, 19

[384] In subcommittee files.
[385] The March 6, 1979, letter from Drs. Pola and Zapf of Hoechst AG is in subcommittee f
[386] In subcommittee files.
[387] In subcommittee files.

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letter from Dr. Waelti who, in noting that Merital-specific antibodies had been found in one fever patient, wrote:

> I think it possible that his further exposure to [Merital] would induce immune reactions. Proper precautions and monitoring certainly are called for.[388]

Dr. J. Gartmann, medical director of the Swiss Drug Monitoring Center, wrote of this same patient in an October 15, 1982, letter to a Hoechst official: "The duration of the process probably varies greatly once the immunological reactions started, as is the case with lung infiltrates."[389] It is noteworthy that Merital's labeling did not mention that lung infiltrates such as alveolitis (i.e., inflammation of the small airsacs of the lung), like hemolytic anemia or fever, may represent an allergic response to the drug until November 1985, more than four years after this letter was written.

In November 1985, FDA *presumed* that a wide range of Merital-associated adverse effects represented allergic responses to the drug. By contrast, in 1983 Hoechst was unequivocally characterizing several reported drug-associated adverse effects—including skin reactions, drug fever, lung infiltrates, yellow discoloration of the skin, and hemolytic anemia—in the West German labeling for the drug as "immunologically caused hypersensitivity reactions."

By late 1983, there were many reports of the various components of Merital's immune toxicity, many associating them as parts of a possible syndrome or syndromes. Throughout most of the NDA review, however, Hoechst made no effort to discuss Merital-associated adverse effects as various manifestations of the drug's toxicity to the human immune system. Instead, the sponsor consistently reported these manifestations as separate and discrete aspects of the drug's toxicity without any reference to the probability that they shared a common immunological origin. Hoechst segregated its reports on drug-associated events such as hemolytic anemia, fever, liver injury, and eosinophilia, never emphasizing that they often occurred in various combinations with one another, or that they collectively could be regarded as various organ manifestations of a "single immunological event." In this connection, Dr. Adkinson has expressed the view that the "regulatory responsibility of the agency was somewhat impaired . . . by the fragmentary documentation of serious allergic reactions which the record indicates the FDA received."[390]

In fact, Hoechst sometimes implied that no such immunological link among various drug-associated adverse effects existed. For example, Hoechst repeatedly downplayed the immunological implications of frequently observed, Merital-associated eosinophilia, which, according to Dr. Adkinson, normally "indicate(s) an ongoing inflammatory or allergic or immunologic reaction of some type or another."[391] In a July 7, 1980, submission, for example, Hoechst informed FDA that "while eosinophilia is often mentioned in the literature in association with drug allergies, there is no evidence that

[388] This letter was included in the sponsor's October 29, 1984, submission to FDA, which is in subcommittee files.
[389] Ibid.
[390] See his September 29, 1986, letter to the subcommittee, Hearing, page 527.
[391] Hearing, page 6.

it has any clinical significance."[392] Eosinophilia accompanied a large fraction of the international fever cases reported in this same submission. Potentially allergic adverse effects reported to FDA in subsequent submissions also commonly involved eosinophilia.

When Hoechst finally acknowledged on October 29, 1984, only two months before FDA approved Merital, that eosinophilia, like several other adverse reactions, probably emanated from a "single immunological event" associated with the drug's use, FDA, by this late date, was already conditioned to overlook the implications of such an acknowledgment. Consequently, on December 28, 1984, Dr Paul Leber wrote that "the eosinophilia is asymptomatic and not linked to any specific clinical syndrome of significance"[393] and FDA approved labeling stating that the "development of eosinophilia did not appear to correlate with abnormal liver function tests fever, hemolytic anemia, or other abnormal laboratory or clinical findings."[394]

F. Hoechst's Failure To Report Safety Information to FDA: An Overview

The subcommittee's investigation revealed that Hoechst neglected to advise FDA prior to Merital's approval of several reports of deaths it received from 1977–1984 suggesting the possibility that Merital was capable of inducing life-threatening allergic reactions. Hoechst also failed to inform FDA prior to Merital's approval of large numbers of other serious drug-associated allergic reactions reported to it from 1982–1984. In addition, the firm withheld data brought to its attention in 1982 indicating that Merital was extraordinarily *immunogenic;* that is, an exceptionally large percentage of Merital patients manifested an immune response to Merital through the development of antibodies to the drug and/or its metabolites. Taken collectively, the information Hoechst failed to disclose to FDA prior to Merital's approval obscured the nature, extent, and severity of the drug's toxicity to the human immune system, and rendered the drug, especially as originally labeled, misbranded within the meaning of the Food, Drug, and Cosmetic Act.

4. FDA'S ENFORCEMENT OF ITS ADVERSE REACTION REPORTING REQUIREMENTS WAS INADEQUATE

FDA Overlooked Clear Evidence of the Sponsor's Failure To Submit Merital-Associated Safety Information

The conclusion that Hoechst did not comply with a wide array of agency adverse reaction reporting requirements is largely based on information contained in FDA's files:

> Reports made to FDA on October 31, 1985, April 24, 1986, and May 15, 1986, contained information clearly indicating that the company *did* not report to FDA, until after Merital

[392] In subcommittee files.
[393] Hearing, page 344. Nonetheless, FDA approved labeling proposed by Hoechst that stated that "[d]rug therapy with Merital (nomifensine maleate) should be discontinued in patients who develop eosinophilia."
[394] In subcommittee files.

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was approved, drug-associated deaths known to the company well before approval.[395]

A post-approval submission made to FDA on November 1, 1985, revealed very large numbers of serious adverse effects—including approximately 60 hemolytic anemia reactions—that were known to the company prior to approval.

Information contained in 15-day alert reports demonstrated non-compliance with the agency's 15-day reporting requirement.

Hoechst's quarterly report for the fourth quarter of 1985 contained at least 100 adverse reactions that were designated as having been reported to the firm during the previous quarter.

Hoechst's October 29, 1984, submission contained a letter from a U.S. consultant stating that "all patients on prolonged therapy develop IgG antibodies to the drug" as well as information showing that, by May 1982, Hoechst had been advised that drug-specific antibodies had been identified in the blood of three Merital patients who had developed hemolytic anemia and eight who had developed fever.

After Chairman Weiss noted that "several Hoechst submissions . . ., on their face, show that the sponsor had not met its adverse reaction reporting requirements," the following exchange took place during the subcommittee's hearing:

> Mr. WEISS. What regulatory action, if any, did FDA take when it received submissions that plainly revealed that the sponsor did not report large numbers of adverse reactions in the timely manner required by law?
>
> Dr. TEMPLE. Well, we didn't take any regulatory action, to my knowledge. But, I'm not sure that we recognized them as being out of compliance.[396]

Hoechst's own submissions provided abundant evidence of its noncompliance with FDA reporting requirements. The committee is concerned that such noncompliance was not "recognized" by FDA prior to the subcommittee's May 22, 1986, hearing.

However, prior to Merital's approval, agency personnel did suspect that the sponsor had not supplied important safety information to FDA in a sufficiently timely manner. In a mid-1984 review, Dr. Thomas Hayes, then the supervisory medical officer for Merital, concerned that the sponsor may have previously withheld data from FDA showing the high degree of fever experienced by some Merital patients, wrote:

> Safety updates were not intended as a panoply behind which adverse events of critical importance (to the approval process) may be hidden. "Full reports" means just what the term conveys.[397]

His superior, Dr. Paul Leber, echoed his sentiments in a December 28, 1984, memorandum:

[395] Additional reports made to FDA following the subcommittee's May 22, 1986, hearing contained similar types of information.
[396] Hearing, page 43.
[397] Hearing, page 44.

> They [Hoechst] have not always provided all information on a particular problem in a timely manner. . . . [T]he apparent delayed expression of our staff's concern about hyperpyrexia is a direct reflection of Hoechst-Roussel's failure to provide all relevant information about this potentially serious risk at an early time.[398]

Despite concerns that the firm did not provide "critical" ar "relevant" safety information in a timely manner, FDA witnes acknowledged at the subcommittee's May 22, 1986, hearing th the matter of the sponsor's reporting practices was not brought the attention of the Division of Scientific Investigations, FDA's i vestigative arm.[399] Nor was any agency investigation undertak when, on February 5, 1985, the subcommittee staff advised the I vision of Scientific Investigations of Dr. Hayes' and Dr. Leber's legations of the sponsor's failure to make timely reports of signi cant safety information.[400] In short, until the subcommittee's M 22, 1986, hearing, FDA had initiated no investigation of the firn reporting practices regarding Merital.[401]

This is not the first instance when the committee has found de ciencies in FDA's enforcement of agency reporting requiremen In a unanimously approved report issued on November 9, 1983, titled *Deficiencies in FDA's Regulation of the New Drug "Orafle* the committee noted that, despite what FDA acknowledged as "full-fledged" and "ongoing" investigation of the reporting pr tices of Eli Lilly and Company, the agency did not undertake inspection of Lilly's international report files concerning deaths sociated with the arthritis drug Oraflex (benoxaprofen) outside t United States until after it had been informed by the subcomm tee that the company had failed to report 13 such deaths to Fl prior to the agency's approval of Oraflex on April 19, 1982.[402] U mately, Lilly pled guilty to criminal charges for failing to make gally required reports of Oraflex-associated deaths to FDA.

On the heels of revelations concerning Lilly's failure to rep drug-associated adverse effects occurring outside the United Stat the committee found that FDA did not conduct any investigat upon learning that Pfizer Pharmaceuticals similarly failed report to FDA at least 26 "serious adverse reactions associa with use of its arthritis drug, Feldene (piroxicam), outside United States" prior to the drug's approval on April 6, 1982.[403]

[398] Hearing, page 45. That Drs. Hayes and Leber did not previously know that Merital been associated with hyperpyrexia or extremely elevated fever (i.e., 40°C or 104°F or abov flects their lack of awareness of information contained in the Merital NDA as well as i medical literature. Two such cases were reported in the U.S. clinical trials, one of which discussed at a December 3, 1981, Psychopharmacologic Drugs Advisory Committee meetin page 155 of the verbatim transcript of this meeting, which is in subcommittee files. The sp also reported on July 7, 1980, 9 international cases of fever of 40°C or more.

In addition, several publications in the world literature reported such cases. See Hunzik al., *Schweiz.med.Wochenschrift*, September 6, 1980; Weihe, Thybo, and Magnussen, *Ugeskri Laeger*, May 18, 1981; Neilsen and Lund, "Drug Fever Due to Nomifensine Treatment i tients with Endogenous Depression," *Int. Pharmacopsychiat*; Nielsen, Lund, Ebert-Peterser Liisbergand, *Ugeskrift for Laeger*, May 18, 1981.

[399] Hearing, page 46.
[400] Hearing, pages 46-7.
[401] See testimony of Dr. Robert Temple, Hearing, page 47.
[402] House Rep. No. 98-511, 98th Cong., 1st Sess., page 18.
[403] Ibid., page 22.

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At that time, the committee concluded that "FDA places the public's health at risk when it does not vigorously enforce the legal requirement that a sponsor report all significant adverse reactions to a new drug under clinical investigation, since this information is needed to weigh the risks of the drug against its potential benefits." [404]

Based on its review of FDA's regulation of Merital, the committee believes that the agency has repeatedly failed to stress to its personnel the need for vigorous enforcement of its reporting requirements. FDA's continuing failure to ensure that sponsors assume the legal consequences for failing to meet these requirements undermines public confidence that the agency is receiving all the information it needs to make informed and responsible decisions about the risks of new drugs.

FDA Misconstrues Its Legal Mandate in Defending Hoechst's Failure To Make Full and Timely Reports of Merital-Associated Safety Information

At time of approval, FDA erroneously thought it had received only 17 reports of hemolytic anemia,[405] a number which Dr. Thomas Hayes, then the supervisory medical officer for the Merital review, characterized as "disturbing" in a June 26-July 2, 1984, memorandum.[406] When asked about Dr. Hayes' statement, Dr. Robert Temple testified: "But, in any event, all he is saying is that it is disturbing. Of course, it's disturbing." [407] Indeed, he testified, "We were worried about the *frequency* and in some cases the severity of the hemolytic anemia." [408] (Emphasis supplied.)

Accordingly, when he was confronted with the subcommittee's finding that the company knew of approximately 100 cases of hemolytic anemia/hemolysis prior to the drug's approval, Dr. Temple initially suggested that, if those reports suggested a change in frequency, the company may have been legally obligated to report them, if not before approval under the IND reporting regulations,[409] at least shortly after approval under the NDA reporting requirements.[410]

[404] Ibid.

[405] In a June 26-July 2, 1984, review, Dr. Thomas Hayes, Group Leader for the Merital review, wrote that 17 such reports had been received, a statement that was repeated in the Summary Basis of Approval for Merital completed after the drug was approved. In subcommittee files. Dr. Temple, however, testified: "I don't think that's right, by the way. I think there were actually a few more than that." Hearing, page 32.

[406] Hearing, page 32.

[407] Hearing, page 34.

[408] Hearing, page 33.

When, however, he was asked to clarify his position, Dr. Temple although earlier stating that 17 reports of hemolytic anemia was "disturbing," minimized the importance of at least 60 or so such cases that FDA never had the opportunity to review before approving Merital:

> Mr. WEISS. Well, assuming that our information is correct, somewhere around 101 or 102 cases had been reported to Hoechst, while you had received 17 or 27 or perhaps 40 or so reports of hemolytic anemia associated with worldwide experience with the drug. Would that difference have been of sufficient significance to have required Hoechst to report all the hemolytic anemia cases known to it?
>
> Dr. TEMPLE. Well, that's relatively close. If we knew of—if the number that they had reported was 40 and if the additional 60 or approximately like that, that's very close to whether it would have made much difference.[411]

The committee believes this view of law enforcement contradicts the letter and spirit of the Food, Drug, and Cosmetic Act. The legal requirement that a sponsor report all significant adverse reactions to a new drug under clinical investigation is designed to ensure that FDA receives all the information it needs to assess a drug's risks prior to determining whether it may be approved for commercial marketing. By publicly minimizing, after approval, the failure to report large numbers of reports of potentially serious adverse

[409] In 1982, Dr. Temple testified that the IND regulations required sponsors to report any substantial increase in frequency of an adverse reaction associated with a new drug under investigation. See Hearings before a Subcommittee of the Committee on Government Operations, "The Regulation of New Drugs by the Food and Drug Administration: The New Drug Review Process," August 3, 1982, page 93.

Despite this, FDA has advised the subcommittee that it had not specifically defined what constitutes a "significant increase in frequency" for an adverse reaction associated with an *investigational* new drug that must be promptly reported to FDA under § 312.1(a)(6) of the agency's IND regulations. See FDA's November 5, 1986, letter to the subcommittee, Hearing, page 4. By contrast, for *approved* drugs, FDA has defined "increased frequency" as an "increase in the rate of occurrence of a particular adverse drug experience, e.g., an increased number of reports of a particular adverse drug experience after appropriate adjustment for drug exposure." See 21 CFR § 314.80(a). FDA currently requires 15-day alert reports for "any significant increase in frequency" of a serious but expected adverse reaction associated with an *approved* new drug. See 21 CFR § 314.80(c)(1)(ii). This section requires sponsors to review the frequency of reports of such reactions "at least as often as the periodic reporting cycle."

[410] Hearing, page 38. Dr. Temple noted, however, that "the IND is not the ideal place to put new reports related to a pending new drug approval because everybody is concentrating on the [new drug] application at that time. So, we have what is called a safety-update, which we ask for just prior to final action. And that's the place to put additional reports that have accumulated." Hearing, page 39. Section 314.50(d)(5)(vi)(b) of the NDA regulations, which did not go into effect until several months after Merital was approved, requires sponsors to "update periodically the pending application with new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling." This requirement, like the IND reporting requirements in general, is not specific as to what sponsors are required to report to FDA. As Dr. Temple acknowledged, "sometimes one can argue about whether a group of events change the overall impression" and, therefore, must be included in a safety update report. Hearing, page 39. Furthermore, unless FDA requests otherwise, sponsors are only required to submit safety updates twice during the history of an NDA—four months after the initial NDA submission and following receipt of an approval letter. Sometimes, as in the case of Merital, several years separate these two points in time. During this interval, it is only to the IND, which, by FDA's acknowledgment, "is not the ideal place to put new reports related to" a new drug under NDA review, that sponsors are generally required to report "significant" safety developments.

[411] Hearing, page 39.

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drug reactions, FDA compromises its ability to review important safety data. Additionally, it sends a signal to sponsors that they need not ensure that FDA is informed of *all* potentially relevant safety data in their possession.

The importance of 60 additional reports of drug-associated hemolytic anemia is significantly enhanced if, as the Merital experience suggests, adverse reactions experienced in other nations may be seriously under-reported, particularly in comparison with the United States. In this connection, the committee notes that for the few months of American marketing, 20 cases of hemolytic anemia were reported among an estimated user population of 100,000 patients.[412] Not included among such cases are several reported as "anemia," "normochromic anemia" or "normocytic anemia," some of which could actually have involved a hemolytic process. If, as often stated, only 1 in 10 adverse drug reactions is ever reported, this would represent an incidence of 2 cases per 1,000 patients, or .20 percent, which is vastly in excess of that claimed from the European experience.

The sponsor's contention that "the occurrence of hemolytic anemia associated with Merital treatment is rare by any standard, with an estimated incidence per million patients months of 1.07," [413] lacks credibility. So, too, does its claim that no hemolytic anemia cases occurred during the U.S. clinical trials.[414] During its limited review of adverse effects reported for those trials, however, the subcommittee staff found at least one clinical trial patient who developed apparent hemolytic anemia [415] in conjunction with fever, and liver damage, including granulomatous lesions in the liver.[416] This case suggests, not only a lack of care in the review of clinical trial data,[417] but also that the incidence of drug-associated hemolytic anemia might be substantially higher than the sponsor claimed was indicated by foreign reporting systems.[418] Dr. Leber's

[412] Seven cases were reported in the January 16, 1986, quarterly report for Merital; 6 cases in the April 24, 1986, quarterly report; and 2 cases in the July 29, 1986, quarterly report; and 4 cases were included in the January 30, 1987, quarterly report. In addition, a possible hemolytic anemia fatality associated with Merital was reported to FDA on February 3, 1987.

[413] See Hoechst's May 7, 1984, submission to the Merital NDA, in subcommittee files.

[414] See, for example, the sponsor's May 7, 1994, submission to the Merital NDA, in subcommittee files.

[415] Dr. Adkinson testified in connection with this case:

> That case interestingly involved a low red blood cell count, a low hematocrit, and had other laboratory values in the case report, an elevated haptoglobin, and increased reticulocyte count and a normal bone marrow aspiration, all of which taken together strongly suggest that a hemolytic process was responsible for the anemia.

Hearing, page 7.

On November 22, 1982, Hoechst also reported to FDA that a U.S. patient receiving Merital as part of the "humanitarian" protocol had a positive Coombs test. In subcommittee files.

[416] Records from the case appear at Hearing, Appendix I. In an August 8, 1977, letter to the sponsor, the clinical investigator wrote: "The liver biopsy itself was suggestive of a type of hypersensitivity reaction . . ." In subcommittee files.

[417] Over the past four years, the committee has twice noted FDA's failure to note important adverse reactions experienced during clinical trials. In *The Regulation of Zomax*, the committee found that FDA had overlooked clinical trial evidence of that drug's association with anaphylactoid reactions. In *Deficiencies in FDA's Regulation of the New Drug Oraflex*, the committee found that FDA was not aware of reports it received of liver and kidney reactions in the clinical trials.

[418] A U.S. incidence of .20 percent translates to 2 cases of hemolytic anemia per 1,000 patients. Although the incidence of hemolytic anemia would increase with time on the drug, it may not be surprising that at least one case of hemolytic anemia occurred among a clinical trial population of more than 1,000 Merital patients.

testimony that Merital-associated hemolytic anemia had been reported at "a vanishingly small rate" before the drug was marketed in the U.S.[419] may reflect the nature of foreign reporting systems.

While factors such as the drug's newness on the market and publicity may have influenced the rate of such reporting, the Merital experience suggests the possibility of particularly significant under-reporting of drug-associated adverse reactions in other nations. If anything, this possibility enhances the significance of Hoechst's pre-approval failure to report to FDA a number of hemolytic anemia cases associated with use of the drug abroad.

Dr. Robert Temple was also reluctant to state that agency reporting requirements had been violated in connection with the sponsor's failure to inform FDA that Merital had been found to be highly immunogenic. When initially asked whether the agency's IND regulations required prompt submission of the finding that Merital had been associated with very frequent antibody formation Dr. Temple testified:

> I would think findings related to antibody formation would be part of what should be submitted. . . . Unless it was completely redundant with other information. And I don't think it was. So, yes, I would say that kind of information is pertinent.[420]

When asked whether "pertinent" meant that the company was legally obligated promptly to report this information, however, Dr. Temple began to retreat:

> Again, I believe that section says that the information—if the information is pertinent to warnings, precautions and so on, it has to be submitted. . . . I would say that information of that kind is somewhat at the margin, because we already knew that antibodies could be formed. . . . [We] would like to know, as part of the review, the details of who is developing antibodies and who is not and how frequent it is and all of those things. But, again in the absence of information linking antibody formation to specific adverse reactions, I think it's debatable whether the finding of antibody formation has to do with warnings, precautions and so on, and therefore requires reports to the IND. . . .[421]

The committee believes it is clear that FDA should require sponsors, at minimum, to bring matters such as the extraordinary immunogenicity of Merital, to its attention. As earlier stated, Merital may have been unique in the degree to which antibodies develop in patients exposed to it. Such information, in suggesting the drug's potential to induce allergic reaction, constituted clinically significant evidence that reactions that appeared to be allergic in nature were, indeed immune-mediated.

FDA's argument that "in the absence of information linking antibody formation to specific adverse reactions" it is "debatable

[419] Hearing, page 35.

[420] Hearing, page 26.

[421] Hearing, page 26.

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whether the finding of antibody formation has to do with warnings, precautions and so on" would mean, for example, that sponsors may not be legally required to submit positive results from an animal carcinogenicity study because comparable human findings have not been observed. Plainly, this has not been the agency's position.

When reminded that Dr. Adkinson had testified that the finding of frequent Merital-associated antibody formation was "significant in assessing Merital's safety," Dr. Temple responded that "Dr. Adkinson is talking now, after the fact, and that helps . . . one judge." [422] However, because FDA was not alerted to the antibody findings for Merital, it did not review their significance "before-the-fact."

Section 505(b) of the Food, Drug, and Costmetic Act requires as part of a new drug application "*full reports* of investigations which have been made to show whether or not such drug is safe for use. . . ." (Emphasis supplied.) In this connection, Mr. William W. Goodrich, then Assistant General Counsel, Department of Health, Education, and Welfare, testified before the subcommittee in 1964:

> The law plainly requires that *full reports* of *all* clinical studies be submitted in the new drug application. Progressively over the years, as we have revised the new drug form and instructions, this has been made more and more emphatic, that the full reports are expected. . . . But the law itself expresses this in terms of full reports of studies bearing on safety.[423] (Emphasis supplied.)

Thus, that same year, John L. Harvey, then FDA's Deputy Commissioner, wrote in connection with the cholesterol-lowering drug MER/29:

> With respect to MER/29 the manufacturer was required to submit to FDA at the time the NDA was submitted or while it was being considered by the FDA and not yet made effective, or when a supplement thereto was filed, all results of investigations and all reports pertinent to an evaluation of the drug's safety.[424]

The "full reports" requirement of law was designed to ensure that FDA has *all* the information it needs to make reasoned, responsible, and independent evaluations of the safety and efficacy of new drugs. Accordingly, any test data involving a new drug that *might* have *any* bearing on the agency's independent assessment of safety and efficacy of a new drug under investigation should and must be promptly reported.

Dr. Temple questioned whether FDA would have found the antibody findings to be "significant" and therefore required to be reported by speculating that FDA may not have altered its view of the drug had it received them:

[422] Hearing, page 27.
[423] Hearings before a Subcommittee of the Committee on Government Operations, "Drug Safety (Part 2)," April 28, 1964, page 601.
[424] See Mr. Harvey's January 7, 1964, letter to Senator Hubert H. Humphrey, Chairman, Subcommittee on Reorganization and International Organizations, Committee on Government Operations, United States Senate.

> But I'm not sure—and it's hard to say in retrospect looking now, I'm not sure it would have made any difference to our conclusions about the drug. That is, mechanism is not what determines what you think about a drug, at least not usually.[425]

But in mandating "full reports," the law clearly did not contemplate speculation by FDA on the significance of "pertinent" information that FDA acknowledges "should [have] be[en] submitted" to FDA prior to its approval of a new drug.

As earlier discussed, at a September 1982 meeting, Hoechst officials were provided data showing frequent antibody formation with Merital. Referring to this meeting, Dr. Temple testified:

> The fact that there were Hoechst employees who were part of that study, I think tells you further that while the mechanism is considered interesting and perhaps important, it is not considered something that tells you, *per se*, without other information, whether the drug has a big problem or doesn't have a big problem.[426]

Absent evidence that the company did not intend to conceal the information from FDA, the committee does not believe such excupatory speculation is warranted. Moreover, any standard that purports to allow companies to determine what safety data are "significant" and therefore required to be reported to FDA, is no standar at all. FDA insists on receiving post-market reports of adverse experiences that sponsors may not consider "drug related" so that can make its own assessment of drug-relatedness.[427] Likewise FDA should not permit companies to preclude it from judging itself whether pre-market investigations of the safety of new drug have yielded "significant" findings.

FDA's policies and statements should make it abundantly clear that sponsors are legally obligated to ensure that the agency can conduct an independent review of all investigations that could possibly bear on the safety of a new drug under review. Agency testimony that speculates whether data it has never seen before would have been found to be "significant" had it been reviewed frustrates Congress' clear intent that the agency be given the opportunity to conduct such a review.

At the time of the subcommittee's hearing, section 312.1(a)(6) of FDA's regulations stated that a sponsor "shall promptly . . . report to the Food and Drug Administration *any findings* associated with use of the drug that *may suggest* significant hazards, contraindications, side-effects, and precautions pertinent to the safety of the drug." (Emphasis supplied.) The "significance" test refers, not to the level of importance attached by FDA upon reviewing a "finding," but rather to the level of importance needed merely to bring the matter to FDA's attention. Thus, the legal standard governing reporting was, *not* that a finding *establishes* "significant hazards, contraindications, side-effects, and precautions pertinent to

[425] Hearing, page 26.
[426] Hearing, page 25.
[427] Section 314.80(a) of FDA's regulations requires sponsors to report any adverse drug experience "whether or not considered drug related."

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safety of the drug," but rather that it "*may suggest*" them. As earlier stated, the committee believes the antibody findings clearly met this standard. However, if FDA determines that the "significance" standard in its regulations is of sufficient ambiguity that it compromises enforcement of the statutory requirement that it receive "full reports" of all safety and efficacy investigations undertaken by a new drug sponsor, the agency should replace it with a standard that clearly places the legal burden on sponsors to ensure that FDA is able to review any data that even remotely can be argued to have a bearing on the agency's assessment of drug safety and efficacy.

5. THE EFFICACY OF MERITAL WAS NOT SUPPORTED BY SUBSTANTIAL EVIDENCE DERIVED FROM ADEQUATE AND WELL-CONTROLLED STUDIES, AS REQUIRED BY LAW

"[I]t was standard textbook knowledge in Germany that Nomifensine was not an effective antidepressant," according to Dr. Peter S. Schoenhoefer, formerly with West Germany's drug regulatory authority.[428] Leading authorities there stated that it is "doubtful" whether the drug had a real antidepressant effect.[429] But under German law, lack of effectiveness does not preclude approval.[430]

Conversely, in the U.S., Congress declared that as a condition of approval, a sponsor provide "substantial evidence . . . consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof." [431]

Dr. Adkinson testified that the risks associated with Merital were of such magnitude that the drug would need to "have a compelling or unique therapeutic benefit in order to justify itself to the medical profession." [432] The committee concludes, however, that the administrative record reflects grossly insufficient evidence of effectiveness for FDA to permit exposure to the unusual panoply of risks presented by the drug.

FDA has long interpreted § 505 of the Food, Drug, and Cosmetic Act to require, as a condition for NDA approval, that efficacy be demonstrated by at least *two* adequate and well-controlled studies.[433] In his testimony before the subcommittee, Dr. Paul Leber,

[428] See his November 19, 1986, letter to the subcommittee, which is in subcommittee files.

[429] See Kuschinsky and Luellmann, *Kurzes Lehrbuch der Pharmakologie and Toxikologie*, Verlag, Stuttgart, 1984, page 294.

[430] In his November 19, 1986, letter, Dr. Peter S. Schoenhoefer wrote:

> It is an annoying fact that approval of a drug license under the provisions of the present German Drug Law does neither prevent nor exclude the licensing of ineffective drugs. . . . Therefore, license was granted to nomifensine by the [German Federal Health] Office in spite of the fact that serious doubts on the efficacy of nomifensine were standard textbook knowledge.

[431] See § 505 of the Food, Drug, and Cosmetic Act.

[432] Hearing, page 8.

[433] Hearing, page 59. This policy emanates from the statutory requirement that efficacy be supported by "adequate and well-controlled investigations" in the plural.

Director, FDA's Division of Neuropharmacological Drug Products, cited three positive studies as the basis for FDA's conclusion that Merital was an effective drug; by investigator name, these were the *Georgia, Meredith* and *Varga* studies.[434]

Dr. Richard Stein, FDA's statistician, however, testified that two of these studies—the *Varga* and *Georgia* trials—did not provide substantial statistical evidence that Merital had a therapeutic effect.[435] Thus, in his judgment, the drug's efficacy was not supported by at least *two* adequate and well-controlled studies, as required by law and established agency policy.

Only *seven* and *nineteen* patients received Merital in the *Varga* and *Georgia* studies, respectively.[436] Early in the review of the Merital NDA, FDA's clinical reviewer cited these small numbers in concluding that these studies could not serve as "pivotal" evidence of the drug's efficacy.[437] Thus, on December 28, 1979, FDA advised the sponsor that Merital was nonapprovable, stating that these "two studies cannot be considered pivotal because the . . . the number of patients in each study was small." [438]

Dr. Temple defended use of the *Varga* study because it was found to yield "statistically significant" results in favor of Merital, notwithstanding that:

> . . . If you were planning a study with the hope of demonstrating an effect, it would probably be imprudent . . . to have fewer than perhaps ten patients on each treatment in it. You would be unlikely to be able to show an effect with a study of that size. . . . So, even though it might have been not the smartest thing in the world to go into a study that was that small, it worked out that there was a statistically significant difference.[439]

Dr. Temple made a similar for the *Georgia* study:

> Mr. WEISS. What additional evidence was submitted by Hoechst to enable this study to be considered sufficiently large to constitute independent pivotal evidence of the drug's effectiveness?
>
> Dr. TEMPLE. I don't think there was any additional statistical evidence. But the study was not too small to show statistical significance. One could make the judgment that it wasn't as big as you wanted it to be to be a pivotal study.
>
> Mr. WEISS. No, we are talking pivotal, right? Pivotal evidence of the drug's effectiveness. That's what you have to have. Isn't that correct? [440]

In its December 28, 1979, *non*approvable letter FDA stated that the sponsor had not submitted at least two studies that were a

[434] Hearing, page 53.

[435] Hearing, page 59.

[436] Hearing, pages 53 and 57.

[437] See, for example, Dr. Hillary Lee's September 14, 1979, review, in subcommittee files. S wrote that these "studies cannot be considered pivotal because . . . the number of patients each study was small.

[438] Hearing, page 371.

[439] Hearing, pages 53-4.

[440] Hearing, page 57.

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ceptable as "pivotal" studies—that is, as studies that served as reliable evidence of the drug's effectiveness. As Dr. Temple recognized at the subcommittee's hearing, the

> . . . word "pivotal" is not the same word "statistically significant," however. That was an expression of doubt [in December 1979] that a study that small should be relied upon.[441]

Reliance on the *Varga* and *Georgia* studies as "statistically significant" cannot be reconciled with the agency's concern with the studies' small numbers—namely, that results from studies with small patient numbers may not be representative of the universe of depressed patients for whom the drug was indicated. Studies showing statistically significant improvement in favor of the drug under review may yield spurious results if they involve insufficient numbers of patients.[442] As Dr. Leber recognized during the third meeting of the Psychopharmacologic Drugs Advisory Committee on Merital:

> . . . If you use a small sample, it is conceivable that you will not have adequately sampled the universe of depressed patients . . . if the sampling is in some way disparate or unusual or not really giving us a good sample, that poses a problem. . . . Small size, however, I think is an important issue.[443]

It is in this context that Dr. Hillary Lee, FDA's clinical reviewer for Merital, stated during the October 15, 1979, meeting of FDA's Psychopharmacologic Drugs Advisory Committee, that she thought the *Varga* study "was not sufficient because . . . the number of subjects was very small."[444]

Thus, several FDA reviewers had cited small sample size as a basis for concluding that the *Varga* and *Georgia* studies *could not be accepted as pivotal evidence* of Merital's efficacy, and, in fact, FDA could not identify a single medical or statistical review that detailed the basis for its conclusion that these trials contained sufficient numbers of Merital patients to serve as pivotal studies.[445]

[441] Hearing, page 54.

[442] In this connection, Dr. Bonnie Camp, Chairperson, Psychopharmacologic Drugs Advisory Committee (PDAC), stated at a February 25, 1983, PDAC meeting on Merital:

> The other question was that when you went away from protocol 308 [which contained the Meredith study], every study that had been presented . . . that was of good significance was a small sample study. . . . [A]re you going to point to studies that have seven subjects in them and say that the drug can be marketed on that basis, and I consider that absurd. . . . I personally want to see 30 subjects in there at least. . . . My personal experience with small sample size has been horrendous. . . . [M]y personal repetitive experience is that the first seven to ten patients you ever get in a clinical study often give you highly significant results, and by the time you've got 50, they are washed out . . .

See the verbatim transcript of the PDAC meeting, pages 122ff., in subcommittee files.

[443] See the verbatim transcript of that February 25, 1983, meeting, page II-139, which is in subcommittee files.

[444] See pages 187-8 of the verbatim transcript of that meeting, which is in subcommittee files.

[445] See FDA's November 5, 1986, letter to the subcommittee, Hearing, page 496. In that letter, FDA, however, stated:

> The size of a study is not ordinarily a standard by which the "pivotal" quality of a study may be judged . . . Nowhere in regulations describing an adequate and well-controlled investigation [21 CFR 314.126] is there any suggestion that a study must be of some particular size.

Continued

FDA regulations require agency personnel to document the basis of every significant FDA decision for the administrative file.[446] Since senior FDA officials had urged that the *Varga* and *Georgia* studies be rejected on the basis of sample size, the committee believes that the supporting evidence leading to the agency's eventual acceptance of these trials should have been appropriately documented in the administrative file.

The *Varga* study was carried out only on geriatric patients, and the *Georgia* study consisted almost entirely of male patients.[447] As a result, FDA reviewers stated on several occasions that the *Varga* study results were not representative of the large numbers of non-elderly patients for whom Merital was also indicated, and the *Georgia* study results could not be extrapolated to women, who comprised the substantial majority of clinical trial patients covered by the Merital NDA.

FDA's statistician, Dr. Richard Stein, testified that the *Varga* study results could not be extrapolated to the non-elderly.[448] And, according to him, additional studies by the sponsor in geriatric patients did not prove Merital's efficacy in this population.[449] Dr. Temple testified that the one geriatric study that was "reviewed in detail" by FDA—the *Cohn* study—"did not provide support at all—all the action was in the Varga group."[450]

When asked whether the sponsor ever provided "adequate statistical evidence for applying the Georgia study to women as well as men," Dr. Richard Stein testified: "In my opinion, never."[451]

Dr. Temple testified that the issue of whether the results of the *Varga* and *Georgia* studies could be generalized to the non-elderly and women, respectively. was "more a clinical concern than a statistical one."[452]

The committee notes, however, that early in the course of the agency's review of the Merital NDA, FDA's clinical reviewers, as well as its statisticians, concluded that the studies were not generalizable and, therefore, had to be rejected as pivotal support of the drug's efficacy. Thus, Dr. Hillary Lee wrote in a September 14, 1979, memorandum:

While FDA's regulations do not define the minimum size needed to attain "pivotal" study status, *in the case of Merital*, several agency reviewers, including the former Associate Director for New Drug Evaluation, rejected the Varga and Georgia studies as "pivotal" evidence of the drug's efficacy on the grounds that they were too small.

[446] See 21 CFR § 10.70 (a) and (b)(1).

[447] Males outnumbered females in the Georgia study 41-9. Hearing, page 58.

[448] Hearing, page 55.

[449] Hearing, page 55.

[450] Hearing, page 55. Dr. Temple testified, however, that another "was said to have been supportive but we didn't review it in detail." Ibid. These additional geriatric studies were completed in 1979 but not submitted to FDA until May 1984, after the sponsor had received its first approvable letter for Merital. Because the sponsor did not submit these studies in support of the drug's efficacy, Dr. Thomas Hayes, Group Leader for the Merital review, wrote in a June 26–July 2, 1984, memorandum: "The geriatric studies now submitted were an attempt to extend or replicate those results. Apparently, it didn't work. We must assume that these studies do not support drug efficacy and add four more studies to the fairly substantial number that don't." Hearing, page 55.

[451] Hearing, page 58. See his presentation beginning at page 71 of the verbatim transcript of the December 3, 1981, meeting of the Psychopharmacologic Drugs Advisory Committee, in subcommittee files. As early as July 16, 1979, Ms. Lucille Pogue, then FDA's statistical reviewer for Merital, noting the largely male make-up of the Georgia study, wrote: "Due to the results o many protocols (and investigators) where most of the patients were females it might be advisable to initiate additional studies to investigate the effectiveness of Merital for males as compared to females." In subcommittee files.

[452] Hearing, page 65.

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> In summary nomifensine has been demonstrated to be effective in three studies . . . in out-patient depressions, one of which involved elderly patients and one, primarily males. The latter two cannot be considered pivotal in that they are not representative of depressions in general.[453]

A few months later, on December 28, 1979, Dr. Marion Finkel, then Associate Director for New Drug Evaluation, notified the sponsor that Merital was not approvable, in part because the *Varga* and *Georgia* "studies cannot be considered pivotal because the patients are not representative of depressions in general . . ." [454] Dr. Finkel, a clinician, was expressing a clinical as well as statistical judgment.

According to Dr. Temple, Dr. Stein's statistical objections represented the only agency non-concurrence in the decision to declare Merital an effective antidepressant. So, the Summary Basis of Approval (SBA) for Merital stated in connection with the *Georgia* study:

> Although the study population is not representative of other studies in the NDA in that there was a preponderance of males in this study, *analyses for the entire NDA indicate that gender was not related to study outcome.*[455] (Emphasis supplied.)

The SBA for the *Varga* study similarly states:

> Although the mean patient age in this study was older than that of depressed patients in general, *analyses of the NDA data show that age was not related to outcome.*[456] (Emphasis supplied.)

FDA, however, never performed any such analyses. Not one agency medical review detailed the basis for FDA's conclusion that the *Varga* study results could be extrapolated to the non-elderly and the *Georgia* study results could be extrapolated to females.[457]

Ultimately, FDA's clinical reviewer decided that Merital had only "a mild antidepressant effect" and wrote that "a more effective antidepressant should produce less equivocal results." [458] Assuming that Merital had only a mild antidepressant effect, Dr. Stein testified that larger studies should have been done to document effectiveness [459] and that "if I were going to do more studies, and I were going to proceed in a practical fashion, I believe I said about fifty patients would be required per treatment group" to demonstrate efficacy.[460] Dr. Stein stated, however, that "Hoechst submitted no studies that I reviewed that had even fifty patients per treatment group. They were all smaller." [461]

[453] In subcommittee files. Also see her comments at pages 187-8 of the verbatim transcript of the October 15, 1979, meeting of the Psychopharmacologic Drugs Advisory Committee, in subcommittee files.
[454] Hearing, page 57.
[455] In subcommittee files.
[456] In subcommittee files.
[457] See FDA's November 5, 1986, response to the subcommittee's July 14, 1986, letter, Hearing, pages 494-5.
[458] Hearing, page 59.
[459] Hearing, page 59.
[460] Hearing, page 59.
[461] Hearing, page 59.

The larger studies that were done on the drug did not demonstrate that Merital performed significantly better than placebo.[462] As Dr. Stein wrote in a memorandum of a March 18, 1986, telephone conversation with the subcommittee staff: "Most of the studies which recruited larger numbers of patients such as those of Goldberg, Kiev, Rickels, Feighner [463] and Hayman provided inconclusive evidence of the effectiveness of Merital." [464]

In fact, Dr. Stein testified that placebo outperformed Merital in many of these studies, and one of them demonstrated the significant superiority of placebo to Merital.[465] Dr. Stein's concerns about this were shared by Dr. Hillary Lee, the clinical reviewer for Merital, who noted in a September 14, 1979, review:

> Here it can be seen that placebo patients achieved more improvement than nomifensine patients in a substantial proportion of the studies. In fact, there were several studies in one protocol where the differences in favor of placebo approached significance and this is disturbing. In addition, of the ten studies with imipramine, nomifensine produced slightly less improvement (never significantly so) than imipramine in eight. . . .[466]

Notwithstanding the problems previously discussed in the studies that FDA ultimately accepted as "pivotal," Dr. Stein testified that if, as he stated in his June 3, 1982, review, the sponsor submitted 17 placebo controlled studies, at least 14 of them did not show statistically adequate superiority of Merital to a placebo treatment.[467]

This led Dr. Stein, in a June 3, 1982, review, to write that the issue of whether the patient population in a study like the *Georgia* trail is sufficiently representative of depressed patients in genera

> . . . is a secondary question which begs somewhat the primary issue whether Merital has any therapeutic effect. The purpose of these studies was to demonstrate the antidepressant activity of Merital.[468]

FDA has interpreted the law to require that NDA approval be based on *at least* two adequate and well-controlled studies support ing effectiveness. Nothing in the law forces FDA to disregard large numbers of negative studies if it has concluded that two such studies have been submitted. In fact, according to Dr. Marion Finkel formerly the Associate Director for New Drug Evaluation, the agency has customarily given considerable weight to negative studies in determining whether efficacy has been demonstrated, as required by law:

[462] Ibid.
[463] Although Dr. Stein included the Feighner trial among those that "provided inconclusi evidence of the effectiveness of Merital," the Summary Basis of Approval for Merital cites th study as strongly supportive of Merital's efficacy. However, 33 of the 57 patients enrolled in t study dropped out before its completion. Dr. Stein testified that such a drop-out rate "would r support statistically reliable evidence" of Merital's efficacy. Hearing, page 60.
[464] Hearing, pages 59-60. See his February 24, 1983, review, in subcommittee files.
[465] Hearing, page 60.
[466] In subcommittee files.
[467] Hearing, page 60.
[468] Hearing, page 58.

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> Although the law requires that we must have studies which show safety and effectiveness, and we have interpreted that to be at least two adequate and well-controlled studies which demonstrate the contribution of the drug to the claimed indications, if, in fact, there are 15 studies which are well-controlled, 13 of which do not adequately show that the drug is effective, and yet the design of the study was sufficient to draw a conclusion as to whether the drug is effective or not, and two investigators have managed to show that the drug is effective, then that is not considered substantial evidence for effectiveness. There has to be a proponderance of evidence among the well-controlled studies that the drug is effective.[469]

Dr. Leber echoed a similar view before the Psychopharmacologic Drugs Advisory Committee on February 25, 1983:

> But we want to get away from this idea that's a little procrustean that all you need to do is find two studies, period, and then walk away, because it is really the idea that there must be a plural of investigations, but the concept that you need only two out of 100 is certainly not there, that you've got two out of two may not be enough. . . . [W]e never pick one or two or two trials out of a whole forest of evidence. We really try to get in some way an integrated sense of what is going on.[470]

The administrative record fails to present documentation that a substantial evidence test has been met when the overwhelming majority of studies demonstrate either no statistically significant superiority to placebo or, in some cases, inferiority to placebo. So, Dr. Leber reportedly advised the sponsor during a January 12, 1983, meeting that its "studies yielded so many divergent results we do not have convincing evidence of efficacy before us which would allow us to approve the drug." [471] Even the sponsor, according to the memorandum of that meeting, "acknowledged that the studies yielded inconsistent efficacy results." [472]

But FDA ultimately found the evidence supporting the efficacy of Merital to be "convincing," prompting Chairman Weiss to observe:

> So, you throw out the 14 tests which, in fact, prove no effectiveness. You take three which, aside from questions about their statistical validity, seem to demonstrate effectiveness, and you say those are the ones that count? [473]

FDA responded that in five of six "three-way" studies comparing imipramine—an approved antidepressant—with Merital and a placebo, imipramine also did not outperform placebo. So, Dr. Temple argued, since

[469] See the verbatim transcript of the May 1, 1980, meeting of FDA's Radiopharmaceutical Drugs Advisory Committee, pages 122-3.
[470] See the verbatim transcript, pages II-21ff. and II-35, in subcommittee files.
[471] Hearing, page 64.
[472] Hearing, page 420
[473] Hearing, page 61.

> . . . no one doubts [imipramine] is effective . . . [and] . . . [i]n five of those six studies . . . it was impossible to distinguish either nomifensine from placebo or imipramine from placebo, . . . [w]hat that tells you is that in five of six seemingly well-designed studies—we don't see any obvious flaws in them—it was impossible to tell the standard therapy that everybody recognizes as effective from placebo.[474]

In short, Dr. Temple testified, the studies lacked "assay sensitivity." [475]

By Dr. Temple's theory, the negative studies did not evidence Merital's ineffectiveness but merely represented failed studies:

> . . . an unsuccessful trial truly gives no information. It is not a negative trial of a drug, especially when the standard agent fails in exactly the same way in the same study. It is no information; it is not negative information.[476]

Under the Food, Drug, and Cosmetic Act, it is not FDA's responsibility to *assume* that a drug is effective, even an approved drug such as imipramine, where a particular study or, in this case, five of six studies, do not support effectiveness. Rather the law requires that a sponsor present "substantial evidence" of effectiveness. That another drug did not fare better than placebo *does not prove* that Merital has been shown significantly superior to placebo, as Dr. Temple acknowledged:

> Mr. WEISS. It sure . . . doesn't mean that [Merital] does work, does it?
> Dr. TEMPLE. It certainly doesn't. . . .[477]

The only three-way study that FDA did not regard as "failed" was, of course, the one trial that appeared to yield positive results in favor of Merital; namely, the *Varga* study. But, as previously discussed, the *Varga* study's small sample size and exclusively geriatric make-up, in the judgment of several agency reviewers, raised serious questions about its representativeness. That five of the six three-way studies were "unsuccessful" would constitute even greater grounds for questioning the legitimacy of the Varga study results.[478]

The committee further notes that many of the negative studies were only two-way studies; they only compared Merital, and not a standard agent, with placebo. If as Dr. Leber wrote on December 28, 1984, a total of 12 negative placebo-controlled studies were performed on Merital, at least six placebo-controlled trials that did not show Merital superior to placebo were two-way, not three-way studies.

[474] Hearing, page 61.
[475] Hearing, page 69.
[476] Hearing, page 61.
[477] Hearing, page 61.
[478] As Dr. John Kane, a consultant to the Psychopharmacologic Drugs Advisory Committee (PDAC), stated before the PDAC on February 25, 1983:

> . . . I wouldn't dismiss the small study statistically, but if it occurs in a series of studies about which concerns are raised as to the design, the methodology, the monitoring, and so forth, and you apply those same concerns to a study with a small sample where a variety of things could have gone wrong, that is what I would be concerned about.

See the verbatim transcript of the PDAC meeting, page II-139, which is in subcommittee file

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In arguing that negative studies for Merital represent "failed" studies and not evidence against the effectivensss of the drug, Dr. Temple assumed that the results of the five three-way studies were applicable to all other negative placebo-controlled trials.

> Just to give a *prediction,* the results of the three-way studies suggest, *if you could assume that the other studies have the same designs and problems,* that when you study nomifensine or imipramine against placebo six times, only one time will you be able to distinguish the active drug from placebo. That's what that would predict *if these studies are all identical.*[479] (Emphasis supplied.)

Even assuming the validity of FDA's position that the three-way studies did not argue against the effectiveness of Merital, Dr. Temple's argument still requires an "assumption" that "all" other negative trials were "identical" to these studies in that they were "failed" studies. Since the law places the burden for demonstrating efficacy on the sponsor, it is simply not appropriate for FDA to be making "assumptions" that enable several negative studies to be considered other than as evidence of the drug's ineffectiveness.[480]

Since the subcommittee's May 22, 1986, hearing, FDA has continued its practice of dismissing substantial amounts of negative evidence. For example, in approving the new drug Buspar (buspirone hydrochloride), an anti-anxiety drug, on September 29, 1986, the agency disregarded several negative efficacy studies submitted for the drug. On May 27, 1986, five days after the subcommittee's hearing, Dr. Temple expressed concern that in the three-way studies submitted to the Buspar NDA, diazepam, unlike Buspar, proved to be a more effective anti-anxiety drug than placebo:

> Unfortunately, the rest of the sponsor's reasonably extensive U.S. study program [other than the Rickels study] has been, to put it charitably, a bust. The difficulty is that . . . there are 4 domestic studies . . . that do not [clearly support the efficacy of buspirone]. More than that, while two of them can probably be considered methodological failures, i.e., "no-test," it is not so clear that the other two are failed studies, and they may actually provide some evidence *against* buspirone. . . . [I]t . . . seems possible that we need another supportive U.S. study prior to approval.[481]

In the three-way studies, diazepam was shown superior to a placebo while Buspar was not. In short, Buspar failed the "assay sensitivity" test that FDA presented as its sole basis for disregarding negative results in the Merital clinical studies program.

[479] Hearing, page 67.

[480] Dr. Esther K. Sleator, a member of the Psychopharmacologic Drugs Advisory Committee (PDAC) who voted against recommending approval of Merital, stated at the Fedruary 25, 1983, meeting of the PDAC:

> . . . I wish you would explain why you accept the validity or the accuracy or the meticulousness of the studies that show efficacy and dismiss those that don't show it as maybe being sloppy or something. Is there a reason for this? I mean, where imipramine was not shown significant would be one rationale, but there's a lot of studies in which the results are negative and which we just have placebo.

See the verbatim transcript of the PDAC meeting, page II-137, in subcommittee files.

[481] In subcommittee files.

In a July 10, 1986, response to Dr. Temple's memorandum on Buspar, with which Dr. Temple later concurred,[482] Dr. Leber wrote:

> Your argument, reduced to its generic state, is that studies failing to provide statistical support for the efficacy of a new drug, especially those studies that have an internally documented sensitivity to detect a drug effect (e.g., three way parallel design studies in which the standard control is significantly superior to placebo) are evidence *against* the efficacy of a new drug. Generally, I do not agree with this interpretation of "negative" studies.[483]

Dr. Leber has abandoned the "assay sensitivity" rationalization that he and Dr. Temple [484] presented as the one reason they could overlook the plethora of negative studies submitted for Merital in declaring that drug to be an effective antidepressant.

In his July 10, 1986, memorandum on Buspar, Dr. Leber concluded:

> [T]he studies failing to provide evidence of efficacy must *not* persuasively contradict the conclusions of the studies identified as positive. I believe there are relatively few results that can be interpreted as convincing evidence of a lack of efficacy. . . . For the moment . . . I'm not sure that we are in a position to interpret with confidence studies that merely fail to discriminate among treatments.[485]

If FDA can find two "positive" studies that it regards as acceptable, it appears that it will disregard, in almost all circumstances, numerous studies in which the drug was not shown superior to placebo. In addition, FDA has subtly shifted the burden of proof for demonstrating efficacy from the NDA sponsor to itself. A sponsor need not submit "convincing evidence" that a drug is effective even when in most trials it has not been shown to be superior to placebo. Instead, FDA has the burden for providing "convincing or "persuasively contradictory" evidence that large numbers of negative studies do evince a "lack of efficacy."

After Dr. Leber decided that Merital had been shown to be an effective antidepressant, he nonetheless stated in a June 11, 1986, memorandum that "[a]t best, Merital has been shown to be a drug with very modest antidepressant effects." [486] To be certain, in the most controlled environments in which the drug's efficacy was investigated—inpatient settings in which patient compliance with protocols requirements could be most tightly monitored—Merital had not been shown to be effective, leading Dr. Leber to conclude that "it may not work in severely ill hospitalized patients." [487] D

[482] In a note dated July 16, 1986, Dr. Temple wrote: "Concur with conclusions." In subcommittee files.

[483] In subcommitee files.

[484] Dr. Leber presented that same "null study" argument that was advanced by Dr. Temple at Hearing, page 66.

[485] In subcommittee files.

[486] Hearing, page 67.

[487] See his June 11, 1984, memorandum, Hearing, page 423.

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spite this, FDA did not require that Merital only be indicated for mild depression.

To Dr. Leber's observation that Merital had been demonstrated "to be a drug with very modest antidepressant effects," Dr. Temple disagreed, emphasizing that only the *"evidence* of effectiveness is modest." [488] Dr. Temple's distinction defies logic. It is data—that is, *evidence*—that FDA always evaluates in determining whether a drug is both safe and effective within the meaning of the law. Moreover, the Food, Drug, and Costmetic Act clearly states that the evidence supporting the efficacy of a new drug not only must be derived from adequate and well-controlled studies, but must be "substantial." The committee cannot imagine how the "substantial evidence" test can be met by evidence that FDA concedes is "modest."

Dr. Leber also testified that because the law requires that evidence of efficacy be evaluated by "experts qualified by scientific training and experience to evaluate the effectiveness" of a new drug, and since the Psychopharmacologic Drugs Advisory Committee that voted in favor of approving Merital consisted of experts, that the test was met.[489] This misconstrues the clear mandate of the Food, Drug, and Cosmetic Act, which speaks *not* to advisory committee experts, but rather to the "expert" qualifications required *by those who conduct the clinical investigations* submitted in support of a new drug's efficacy and safety. So, Section 505(d) of the Food, Drug, and Cosmetic Act requires sponsors to submit " 'substantial evidence'. . . consisting of adequate and well-controlled *investigations . . . by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved . . .*"

FDA's own records are replete with additional statements by its own personnel that "substantial evidence" had not materialized from the data generated by the sponsor's clinical program.

In a July 16, 1979, review, Dr. Lucille P. Pogue, an agency statistician, wrote:

> Based on the statistical evaluations of the eleven protocols with placebo control group it appears that this submission presents suggestive but not substantial evidence of the superiority of Merital as compared to placebo for patients who manifest various symptoms of depression.[490]

On September 14, 1979, Dr. J. Hillary Lee, the clinical reviewer for Merital, wrote that it is

> not possible to identify "more than one adequate and well controlled trial which demonstrates substantial evidence of efficacy," the criterion for approval.[491]

In a December 13, 1979, review, agency statistician Jerome Senturia wrote:

[488] Hearing, page 67.
[489] Hearing, page 63.
[490] In subcommittee files.
[491] In subcommittee files.

> This submission does not contain substantial evidence of the efficacious and safe use of nomifensine maleate in the management of depression.[492]

In FDA's December 28, 1979, nonapprovable letter, Dr. Marion J. Finkel, then Associate Director for New Drug Evaluation, FDA's Bureau of Drugs, advised the company:

> [T]he NDA does not contain "substantial evidence consisting of adequate and well-controlled investigations," a criterion for approval." [493]

In a December 23, 1980, review, Dr. Donald A. Pierce, a consultant to FDA from Oregon State University, wrote:

> In my opinion there is not substantial evidence for general efficacy of Merital, compared to placebo,[494]

a conclusion with which FDA statistician, Dr. Richard Stein, concurred in a January 14, 1981, review:

> I am in agreement with Dr. Pierce that substantial statistical evidence is lacking for the general efficacy of Merital.[495]

In a November 23, 1981, review, FDA's clinical reviewer, Dr. J. Hillary Lee, wrote:

> The main issue with this NDA is to determine whether there is more than one study showing substantial evidence of efficacy. . . . This submission continues to have one pivotal study (Meredith) and two strongly supportive studies of restricted generalizability (Georgia-males and Varga-elderly).[496]

Even Dr. Leber, according to a memorandum of a July 20, 1982, meeting, expressed "severe doubts of whether the drug is an effective antidepressant" [497] and reportedly informed the sponsor at a January 12, 1983, meeting that "[w]e would be troubled if this drug were approved when effective drugs are available." [498]

In light of the persistent doubts expressed by agency clinicians and statisticians alike, Dr. Leber also advised the sponsor in July 1982 that "[w]e cannot conclude the drug is effective based on studies presented to date." [499] Nonetheless, as FDA acknowledged in its appearance before the subcommittee, the agency's decision to declare Merital effective was based on studies included in the original NDA submission of December 1978 and not on any additional studies submitted after that meeting.[500] In the six years that FDA spent analyzing and re-analyzing the questionable efficacy data submitted in support of Merital's efficacy, the agency did not re-

[492] In subcommittee files.
[493] Hearing, page 371.
[494] In subcommittee files.
[495] In subcommittee files.
[496] In subcommittee files.
[497] Hearing, page 67.
[498] Hearing, page 67.
[499] Hearing, page 68.
[500] Hearing, page 68.

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quire the firm to conduct any additional studies to determine whether the efficacy data met the requirements of law.

When the Psychopharmacologic Drugs Advisory Committee first met to discuss Merital on October 15, 1979, more than *five years* before Merital was approved, it recommended that additional studies be considered if re-analysis of the efficacy evidence upon subsequent pooling of the data did not show substantial evidence of effectiveness.[501] When re-analysis of subsequent data poolings did not yield favorable results in support of the drug's efficacy, the firm still was not required to conduct additional studies.

In view of the agency personnel's persistent reservations about whether "substantial evidence" of efficacy had been demonstrated, the record lacks support for FDA's failure to have required the sponsor to perform new efficacy studies for submission to the Merital NDA.

During his testimony before the subcommittee, Dr. Leber made a revealing comment about the agency's apparent perspective on the new drug review process for Merital:

> The first thing we did after that—this was back in December 1981—was to have a meeting *to figure out how to approve this drug,* because the advisory committee had looked at the evidence, having first turned it down in 1979, and now said it was positive.[502] (Emphasis supplied.)

The statement describes what becomes clear after examining the history of the agency's review of Merital's efficacy; namely, that rather than require the firm to produce the kind of "substantial evidence" required by law, FDA spent many years re-analyzing the same set of questionable data in an effort "to figure out how to approve this drug."

Congress did not authorize FDA, in its review of new drug applications, to engage in any function other than assuring that sponsors have demonstrated new drugs *safe* and *effective* within the meaning of the law. While FDA is expected to process new drug applications in an efficient and economical manner, it is not the agency's function to try to devise means by which new drugs may be approved.

6. FDA'S LATE DECEMBER APPROVAL OF MERITAL REFLECTS PRESSURE TO MEET INAPPROPRIATE END-OF-THE-YEAR DEADLINES

In recent years, FDA has approved a disproportionate number of new drugs during the month of December. Of the 22 new molecular entities approved in 1984, seven (31.8 percent), including Merital, were approved in December.[503] Of the record number of 30 new molecular entities that FDA approved in 1985, 16 (53.3 percent) were approved in December.[504] Forty (30 percent) of the 133 new chemical entities approved since 1980 were approved in December.[505] By contrast, only 1 (0.8 percent) of these 133 drugs was approved in the month of January.[506]

[501] See pages 230-1 of the verbatim transcript of this meeting, in subcommittee files.
[502] Hearing, page 62.
[503] Hearing, page 69.
[504] Ibid.

FDA frequently cites its record number of new drug approvals as a sign of its progress in improving new drug review procedures.[507] But the subcommittee raised questions during its hearing about this flurry of activity in December and FDA's desire to improve its "annual scorecard."[508] FDA maintained that large numbers of December approvals reflect companies' desire to meet end-of-the-year deadlines rather than an agency program to improve yearly scorecards.[509]

The administrative record in the Merital case, however, suggests otherwise. On August 1, 1984, FDA advised Hoechst that, in view of Merital's unusual panoply of risks, the drug could only be approved as "second-line" therapy.[510] A week later, FDA's medical reviewer told the sponsor that he did not believe "we would be receptive to approving the drug" without limiting it to "second-line" use.[511] On October 31, 1984, Hoechst objected, stating that such a step "virtually precludes the marketing of this drug."[512]

This and all other "outstanding issues" were resolved during a lengthy teleconference on December 21, 1984. As agreed during this teleconference, Merital was approved ten days later *without a "second-line" restriction on its use.*[513]

Dr. Temple rejected the suggestion that in late December 1984 FDA "walked away from, or bowed to, the company's objection to [FDA's] determination that Merital should be labeled as a second-line drug."[514] Dr. Temple testified that FDA decided that it "didn't have a basis" for requiring Merital to be restricted to "second-line use," but that "had we pressed that point and insisted on it, the company would have accepted second-line labeling."[515] As the end of 1984 approached, FDA was prepared, if necessary, to tell Hoechst to "[t]ake it or leave it."[516]

Although FDA's regulations require documentation of all significant contacts with the regulated industry,[517] no memorandum was prepared of the agency's December 21, 1984, teleconference with Hoechst.[518] The only record of this important contact was prepared by Hoechst officials. According to their account, Dr. Paul Leber of FDA told the company that "FDA was determined to re-

[505] Ibid.
[506] Ibid.
[507] For example, in *Summary of Significant Accomplishments and Activities in 1985,* the agency stated: "In 1985, FDA approved 30 new chemical entities. This total surpassed the previous record of 28, and was 12 more than the number of NCEs approved in 1984."
[508] Hearing, page 71.
[509] Hearing, page 70.
[510] FDA's August 1, 1984, letter is in subcommittee files.
[511] Dr. Thomas Hayes' memorandum of an August 7, 1984, telephone conversation with the sponsor is in subcommittee files.
[512] Hearing, pages 350-2.
[513] Hearing, page 487.
[514] Hearing, page 73. Dr. Temple testified that "we made the conclusion some time before" December 1984.
[515] Ibid.
[516] Hearing, page 73.
[517] See Section 10.65 of FDA's regulations.
[518] See FDA's November 5, 1986, letter to the subcommittee, Hearing, page 487. FDA has advised the subcommittee that "[b]ecause in this instance there was a substantive contact with a person outside the Agency, a specific memo of the telephone conversation should have been prepared." Ibid.

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solve the Merital NDA before the end of 1984." In fact, FDA apparently informed the company that it planned to approve the drug on December 31, 1984, as it eventually did.[519] Hoechst characterized FDA's abandonment of its insistence that Merital be approved as second-line therapy as a "concession" that "satisfies [Hoechst's] minimal needs for a marketable drug. . . ." [520]

The record amply reflects that it was FDA's determination to approve the Merital NDA by the end of 1984, not the firm's desire to meet an end-of-the-year deadline, which drove the approval process for the drug and may have been responsible for FDA's abrupt decision in late December 1984 to drop its insistence that Merital be marketed only as "second-line" therapy.

FDA is prohibited by law from approving new drugs unless they have been shown to be safe and effective and their labeling bears adequate directions for use. It is imperative that the agency ensure that its approval actions are not influenced by arbitrary, self-imposed, end-of-the-year deadlines.

V. Recommendations

The committee recommends that the Secretary of Health and Human Services take prompt action to assure the correction of the deficiencies identified in this report. The committee specifically recommends that:

1. FDA ensure timely receipt and review of all important publications in the world literature pertinent to evaluating the safety and efficacy of a new drug under review, including translations of all such publications appearing in foreign languages. In this regard, FDA should require its scientists to review relevant bibliographical listings from the Medical Literature Analysis and Retrieval System (MEDLARS) concerning such drugs, particularly before approving them for marketing.

2. FDA require sponsors to submit information relating to the marketing and investigation of new drugs under review in the United States, including

   (a) all labeling approved by foreign regulatory agencies;

   (b) all standardized warning or information letters distributed to practitioners, pharmacists, and other health professionals in foreign nations; and

   (c) accounts of all important regulatory developments concerning such drugs in foreign countries.

3. FDA ensure that sponsors submit to it *timely* and *full* reports of *all* information in their possession possibly bearing on the safety of a new drug under review. FDA should take steps to ensure that its personnel correctly interpret and strictly enforce all legal adverse reaction reporting requirements.

4. FDA amend its adverse reaction reporting regulations to

[519] See the December 26, 1984, letter from officials in Hoechst's U.S. affiliate to the parent firm in Germany, in subcommittee files. In their December 26, 1984, account of their December 21, 1984 teleconference with FDA, Hoechst officials wrote that the company "expects Merital NDA approval on December 31."

[520] Ibid.

   (a) require timely reports of *all* deaths, whether or not "unexpected," associated with the foreign use of a new drug approved for marketing in the United States;

   (b) precisely define a "significant increase" in the frequency of an adverse effect reported for a new drug under investigation that must be promptly brought to the agency's attention.

5. FDA prevent the marketing of any new drug whose efficacy is not supported by "substantial evidence" derived from "adequate and well-controlled" clinical studies, as required by Section 505(d) of the Food, Drug, and Cosmetic Act. In determining whether such evidence has been provided, FDA should give appropriate weight to all controlled clinical trials that demonstrate, or fail to demonstrate, the drug's efficacy for its intended use.

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Exhibit C

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Union Calendar No. 634

100th Congress, 2d Session - - - - - - - - - - House Report 100-1086

FDA'S DEFICIENT REGULATION OF THE NEW DRUG VERSED

SEVENTY-FIRST REPORT

BY THE

COMMITTEE ON GOVERNMENT OPERATIONS

together with

ADDITIONAL VIEWS

OCTOBER 13, 1988.—Committed to the Committee of the Whole House on the State of the Union and ordered to be printed

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LETTER OF TRANSMITTAL

HOUSE OF REPRESENTATIVES,
Washington, DC, October 13, 1988.

Hon. JIM WRIGHT,
Speaker of the House of Representatives,
Washington, DC.

DEAR MR. SPEAKER: By direction of the Committee on Government Operations, I submit herewith the committee's seventy-first report to the 100th Congress. The committee's report is based on a study made by its Human Resources and Intergovernmental Relations Subcommittee.

JACK BROOKS, *Chairman.*

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Calendar No. 634

100TH CONGRESS
2d Session

HOUSE OF REPRESENTATIVES

REPORT
100-1086

FDA'S DEFICIENT REGULATION OF THE NEW DRUG VERSED

OCTOBER 13, 1988.—Committed to the Committee of the Whole House on the State of the Union and ordered to be printed

Mr. BROOKS, from the Committee on Government Operations, submitted the following

SEVENTY-FIRST REPORT

together with

ADDITIONAL VIEWS

BASED ON A STUDY BY THE HUMAN RESOURCES AND INTERGOVERNMENTAL RELATIONS SUBCOMMITTEE

On September 27, 1988, the Committee on Government Operations approved and adopted a report entitled "FDA's Deficient Regulation of the New Drug Versed." The Chairman was directed to transmit a copy to the Speaker of the House.

I. INTRODUCTION

Under the rules of the House of Representatives, the Committee on Government Operations has responsibility for studying the operation of Government activities at all levels. The committee has assigned this responsibility as it relates to the Department of Health and Human Services (HHS) to the Human Resources and Intergovernmental Relations Subcommittee.

Pursuant to its ongoing oversight of FDA's regulation of new pharmaceutical products, the subcommittee in 1987 undertook a review of FDA's regulation of the new drug Versed (midazolam hydrochloride), an anesthetic and sedative manufactured by Hoffmann-La Roche Inc. (or Roche) of Nutley, New Jersey, a subsidiary of F. Hoffman-La Roche & Company Ltd. of Basle, Switzerland.

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FDA approved Versed on December 20, 1985, for preoperative sedation, induction of general anesthesia, and conscious sedation [1] for short diagnostic or endoscopic procedures.[2] For preoperative sedation, the drug is administered by an intramuscular injection; for conscious sedation and general anesthesia, it is given intravenously.

Since it was approved for marketing, Versed has been associated with numerous reports of respiratory and cardiac arrest,[3] a high percentage of which have involved deaths. Most Versed-associated cardiorespiratory fatalities have occurred in elderly patients, primarily in connection with the drug's use for conscious sedation in endoscopy settings where patient monitoring and emergency resuscitation capacities have been inadequate.

The subcommittee's investigation included public hearings on May 5 and 10, 1988.[4]

II. Background

Roche submitted an investigational new drug (IND) application for intravenous [5] midazolam on September 26, 1975.[6]

On September 15, 1982, Versed was introduced to the worldwide market in Switzerland, the home of Hoffmann-La Roche. Three months later, Hoffmann-La Roche submitted its new drug application (NDA) for Versed to FDA.[7] On January 1, 1983, Versed entered the U.K. market.[8]

[1] Conscious sedation, as the name implies, involves a patient who is sedated but remains conscious and can speak and, where necessary, cooperate with the physician.

[2] Endoscopies involve inspections of bodily cavities by means of special scopes. These entail gastroscopy (inspection via an instrument that passes down the throat through the esophagus into the stomach), bronchoscopy (inspection via an instrument that passes through the larynx down into the trachea and into the bronchii of the lungs), colonoscopy (inspection via an instrument that is inserted past the anus through the rectum into the colon), and cystoscopy (inspection via an instrument inserted through the urethra of the penis into the bladder). Versed is also indicated for conscious sedation during coronary angiography and cardiac catherization.

[3] Patients have often experienced cardiac complications following a severe episode of Versed-associated apnea and respiratory arrest. Versed-induced respiratory and cardiac depression lead to diminished oxygen saturation of the blood. One published study reported a decline in oxygen desaturation rates to below 80 percent in 7 percent of patients given Versed during a gastroscopy, which was of "considerable concern" to the authors because "cardiac arrhythmias are particularly liable to occur at times of hypoxaemia (decreased oxygen in the blood)." See Bell, Reeve, Moshiri, Morden, Coady, Stapleten, and Logan, "Intravenous midazolam: a study of the degree of oxygen desaturation occurring during upper gastrointestinal endoscopy," *Brit. J. Clin. Pharmacol.* 23: 703, 1987. Versed suppresses the normal drive or signal to breathe in the presence of accumulating, excess carbon dioxide. See Alexander and Gross, "Sedative Doses of Midazolam Depress Hypoxic Ventilatory Responses in Humans," *Anesth. Analg.* 67: 377, 1988.

[4] Hearings before a Subcommittee of the Committee on Government Operations, "FDA's Regulation of the New Drug Versed," May 5 and 10, 1988, hereafter referred to as Hearing(s).

[5] An IND application for an intramuscular version of midazolam was submitted on June 26, 1980.

[6] The application was assigned to FDA's Division of Neuropharmacological Drug Products. It was transferred to the agency's Division of Surgical-Dental Drug Products on September 16, 1977.

The IND was submitted for the maleate salt of midazolam. This maleate formulation was later changed to a hydrochloride solution, which was thereafter employed in clinical investigations. FDA subsequently regarded the hydrochloride solution as clinically equivalent to the maleate solution.

[7] Summaries from Roche's December 15, 1982, submission of the Versed NDA are in subcommittee files.

[8] It was first marketed in the U.K. for use in conscious sedation. It was not until 1985 that Versed was approved in the U.K. for intramuscular preoperative sedation and for the induction of general anesthesia.

On March 1, 1984, the drug was launched onto the West German market. In May 1985, it was introduced to the Swedish market.

The Versed NDA and IND were reviewed by two FDA divisions, the Division of Surgical-Dental Drug Products and the Division of Neuropharmacological Drug Products. On December 20, 1985, three years after the NDA was submitted, FDA approved Versed for U.S. marketing.[9]

Versed is a member of the benzodiazepine family of drugs, as is Valium (diazepam), another Roche drug which, in its injectable form, is also indicated for conscious sedation.[10] However, Valium, unlike Versed, is not indicated for general anesthesia.

Depression of the respiratory center is a known adverse effect of the benzodiazepines,[11] and is often dose-related; that is, the risk increases with dose. The risk of respiratory depression is particularly enhanced when Versed is used in conjunction with central nervous system depressants, particularly narcotic analgesics such as Demerol (meperidine).[12]

Shortly after U.S. marketing of Versed commenced on March 19, 1986, Roche's U.S. affiliate began to receive reports of serious and frequently fatal cardiorespiratory reactions associated with the drug's use. On April 14, 1986, for example, Roche received the report of the death of a 60-year-old German man who received 7 mg. of Versed before a colonoscopy.[13]

On April 23, 1986, approximately one month after U.S. marketing began, Roche received the first report of a fatal reaction associated with American use of the drug.[14] The case was submitted to FDA as a 15-day alert report on May 13, 1986.

On May 13, 1986, Roche also received information from its Basle, Switzerland, parent on 6 fatal and 19 nonfatal cases of drug-associated respiratory depression and/or cardiotoxicity, most of which were associated with the drug's use for conscious sedation.[15] Four of these fatal and 10 of these nonfatal cases had not been previously reported to FDA.[16]

Two days later, a Roche representative phoned Dr. David L. Scally, FDA's medical reviewer for Versed, to discuss possible revi-

[9] FDA advised Roche that Versed was approvable on November 8, 1985. Around that time, FDA apparently informed the firm that the drug would be approved before the end of the year, since, on November 20, 1985, two Roche officials wrote that "we have learned recently that Versed will be FDA approved by January 1, 1986." See May 5 Hearing, galley page 30. On the inappropriateness of FDA's establishment of end-of-the-year deadlines for new drug approvals, see *FDA's Regulation of the New Drug Merital*, House Rep. No. 100-206, Fifteenth Report by the Committee on Government Operations, 100th Cong., 1st Sess., July 8, 1987, pages 92-4.

[10] Versed is generally claimed as having some advantages over Valium, including a quicker onset of sedation, less patient recall of the events preceding (i.e., retrograde amnesia) and following (i.e., anterograde amnesia) unpleasant procedures. Because it is water soluble, it also produces less vein irritation (thrombophlebitis) than the version of Valium marketed in the United States. In Europe, the Diazemuls version of diazepam is marketed in an emulsion solvent which, unlike the U.S. formulation utilizing a propylene glycol solvent, does not typically cause vein irritation.

[11] See the testimony of Dr. Alan Lisbon, Assistant Professor of Anesthesia, Harvard Medical School, and Co-Chairman, Respiratory-Surgical Intensive Care Unit, Beth Israel Hospital, Boston, May 5 Hearing, galley page 22.

[12] Accordingly, the labeling for Versed has consistently recommended a 25 to 30 percent reduction in dose when narcotics are also used.

[13] Records on this case are in subcommittee files. The case was reported to FDA as a 15-day alert reaction on May 1, 1986. The patient eventually experienced cyanosis and respiratory failure. The .159 mg/kg dose he received was regarded as "a very high dose for sedation" since he had a history of respiratory insufficiency.

[14] The case involved a 67-year-old male who became agitated after receiving Versed intramuscularly for an endoscopy. Records on this case are in the subcommittee files.

[15] May 5 Hearing, galley page 67.

[16] May 5 Hearing, galley page 67.

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sions in the labeling instructions governing the drug's use for conscious sedation.[17]

On May 30, 1986, two weeks after this telephone call, the Drugs Commission of the German Medical Profession published a warning on Versed-associated apnea (cessation of respiration) and cardiac arrest.[18] The May 30, 1986, *Deutsches Artzeblatt* article entitled, "Take Care When Giving Midazolam!," was based on reports of fatal cardiorespiratory reactions to the drug.[19] By this time, Roche had received another U.S. report of a fatal reaction to Versed.[20]

On June 3, 1986, Roche notified FDA of eight of the serious cases of respiratory depression associated with Versed's foreign marketing that were reported to it by its Swiss parent on May 13, 1986, five of which involved fatalities.[21]

On June 20, 1986, Roche proposed revisions to the package insert for conscious sedation.[22] Versed's originally approved labeling recommended that, for conscious sedation, the drug be "titrated" or slowly injected to the point where patient speech is slurred. The labeling further stated that "[g]enerally 0.1 to 0.15 mg/kg" of Versed "is adequ[illegible], but up to 0.2 mg/kg may be given, particularly when concomitant narcotics are omitted."[23] Roche now proposed clarifying 0.1 and 0.15 as *total* doses and, for the first time, suggested that patients be given an initial titration dose of 2.5 milligrams, to be administered over 2 to 3 minutes.[24]

In view of the serious cardiorespiratory reactions to Versed that had recently been reported, FDA wrote officials in West Germany, France, and Switzerland on July 7, 1986, to inquire about their experiences with the drug.[25]

That same day, Dr. Russell Katz, a medical officer in FDA's Division of Neuropharmacological Drug Products, completed a review of reports received of foreign and domestic cardiorespiratory reactions to the drug.[26] In three domestic cases he characterized as "strongly suggestive of a drug effect," Dr. Katz noted that the

> . . . doses [used] were within the currently recommended dose ranges, even considering the fact that these patients had certain "risk" factors. . . . It should be pointed out that two of the domestic cases both experienced fatal events . . . after having been given Versed in doses that would (probably) have been consistent with the new dosing recommendations.[27]

On August 1, 1986, *The Medical Letter on Drugs and Therapeutics* reported that it had been advised by consultants that "the manufacturer's current dosage recommendations for midazolam may be too high for some patients."[28]

On September 10, 1986, Dr. Scally, a medical officer with FDA's Division of Surgical-Dental Drug Products, noted this statement[29] in his first review of post-market reports of adverse reactions associated with domestic and foreign use of Versed. He concluded in that review that physicians using Versed, not the drug itself, were principally responsible for the adverse outcomes reported for the drug:

> It is not surprising to see cases of underventilation or apnea following i.v. administration of a drug which is suitable in larger doses for induction of general anesthesia. I therefore conclude that some practitioners who use midazolam to facilitate endoscopy are not competent by training and/or preparation to administer i.v. drugs which may depress respiration.[30]

Dr. Scally echoed this view in a proposed "Dear Doctor" letter concerning Versed he drafted on October 1, 1986, more than four months before Roche first distributed such a letter to U.S. physicians. That draft letter began:

> Preliminary data on five U.S. cases of respiratory and cardiac arrest and 6 worldwide suggest that endoscopists and others may not be fully aware of the preparation needed prior to use of midazolam. The high mortality—over 80 percent—dictates that a reminder is indicated.[31]

On October 18, 1986, Roche representatives informed several outside anesthesiologists serving on the company's advisory board for Versed that the firm had been barraged by reports from endoscopists of oversedation and respiratory depression associated with the

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[17] Ibid. There is no record that Dr. Scally was told during that call that just two days earlier Roche had received from its Swiss parent several reports of respiratory depression and cardiotoxicity, including fatalities, generally associated with the drug's use for conscious sedation. In addition, Dr. Scally testified that he did not recall receiving such information during that telephone conversation. Ibid.

[18] FDA did not learn of this publication until well over a year later. Dr. Scally asked Roche for it on *July 10, 1987*—more than one year after it was published—and it was sent to FDA on *August 19, 1987*. May 5 Hearing, galley pages 67-8.

[19] Ibid.

[20] On May 22, 1986, Roche received the report of a 73-year-old woman who died from respiratory arrest after receiving 2 mg or .045 mg/kg of Versed for a colonoscopy. The case was reported to FDA as a 15-day alert report on June 12, 1986. Records on this case are in subcommittee files.

[21] May 5 Hearing, galley page 68. Only one of these five had previously been reported to FDA and then had only been briefly summarized in a July 26, 1985, submission to FDA. Ibid.

[22] May 5 Hearing, galley page 71.

[23] The labeling, however, advised dosage reductions of 25 percent to 30 percent "if narcotic premedication is used." It also stated that "[p]atients 60 years or older may require doses lower by about 30% than younger patients." Hearings, Appendix I.

[24] Hearings, Appendix I.

[25] FDA's July 7, 1986, letters are in subcommittee files.

[26] Dr. Katz's July 7, 1986, review is in subcommittee files.

[27] Ibid.

[28] The review article in the August 1, 1986, issue of *The Medical Letter on Drugs and Therapeutics* on "Midazolam" is in Hearings, Appendix I.

[29] Dr. Scally observed that "[t]here has been speculation that current dosage recommendations for midazolam may be too high for some patients, especially the elderly." Accordingly, he recommended that the "sponsor might be asked if more specific dosage experience in the elderly has accumulated since the original submission of the new drug application." Dr. Scally's September 10, 1986, review is in subcommittee files.

In an April 12, 1985, review of 12 pharmacokinetic studies, which is in subcommittee files, Paul Hepp, FDA's Pharmacokinetics Evaluation Branch, concluded that Versed "has not been found acceptable to the Division of Biopharmaceutics" in part because "the data presented on pharmacokinetics in elderly persons is extremely weak." The one pharmacokinetic protocol for the elderly, he continued,

> . . . looked at patients in their *fifties* and all females at that. Benzodiazepines might be *expected* to show gender dependency and the rather significant increases in volume of distribution and half-life might become very pronounced in older individuals. Though both might be termed "elderly", there are big differences between most 55 year olds and 80-85 year olds and the term "elderly" requires explanation.

[30] In subcommittee files.

[31] In subcommittee files.

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drug's use for conscious sedation,[32] many of whom, according to one Roche representative, "seem to be giving too much [Versed] too quickly. . . ." [33] By this time, Roche had received reports of over a dozen Versed-associated deaths.

On November 14, 1986, Dr. Janet Arrowsmith and Mr. David Barash, both of FDA's Office of Epidemiology and Biostatistics, wrote that since marketing FDA had received 29 reports of serious cardiorespiratory reactions to Versed, 17 of which involved deaths.[34] They further noted that "[w]ith one exception, patients received acceptable doses of the drug, except that some were receiving additional central nervous system depressants."[35]

In a November 19, 1986, review, Dr. David L. Scally, FDA's medical reviewer for Versed, noted that half of the clinical trial cases of Versed-associated apnea reported to the Versed IND appeared to have been "severe" or "moderately severe"; that is, countermeasures were required to insure adequate ventilation.[36] By contrast, all of the apnea cases reported to the Versed IND for clinical trial patients given Valium appeared "mild".[37] Dr. Scally concluded that it "would appear that i.v. midazolam is a bigger threat to adequate ventilation than is i.v. diazepam when administered slowly to the same endpoint of slurred speech."[38]

In a November 26, 1986, review of U.S. adverse reaction reports for Versed, Dr. Robert Temple, then Director of FDA's Office of Drug Research and Review, found several "reasonably plausible" cases of drug-induced cardiorespiratory toxicity, which, while constituting what he regarded as only a "weak signal," nonetheless warranted a "Dear Doctor" letter that provided "a prompt reminder to physicians about the need to observe particular care in using midazolam."[39]

A few days later, the safety of Versed was the subject of a meeting of FDA's Anesthetic and Life Support Drugs Advisory Committee. At that December 1, 1986, meeting, a Roche representative stated that "we think endoscopy is where the problem is." [40] FDA's medical reviewer for Versed, Dr. David Scally, also remarked that the:

> . . . clinicians may have used [Valium] without the same sort of problems that they are getting into with [Versed]. I can't prove that but it looks that way. . . . [41]

[32] Roche officials stated at that meeting, according to a tape recording obtained from Hoffmann-La Roche:

> Our major problem is dosing. We have oversedation, agitation—it's more potent than was reported. . . . All the reports that we're getting back are really from endoscopists. People calling on endoscopists to say, I gave that to a patient, they were apneic [i.e., unable to breathe] or they stopped breathing, or they went into an arrest or whatever it might be, and now we're going to go back to Valium.

Hearings, Appendix I.

[33] See the transcript of this meeting, Hearings, Appendix I.

[34] Eighteen of the 29 reports were domestic and 11 were foreign.

[35] Their November 14, 1986, memorandum is in subcommittee files.

[36] In subcommittee files. Dr. Scally was asked to review the Versed IND for apnea cases at a November 6, 1986, internal FDA meeting.

[37] Ibid.

[38] Ibid.

[39] In subcommittee files.

[40] See the statement of Roche's Dr. Philip Del Vecchio in the verbatim transcript of that meeting, page I-69, which is in subcommittee files.

[41] See page I-63 of the verbatim transcript of that meeting, which is in subcommittee files.

In addition, advisory committee member, Dr. Casey Blitt, informed the meeting attendees that his hospital had had "at least a dozen near misses in the first month" of the drug's marketing and that "as soon as we dropped the dose to at least half, if not more, the problem immediately disappeared." [42] He, therefore, opined that the doses recommended in the Versed package insert were too high.

Two weeks following the advisory committee meeting, FDA requested that Roche provide special bimonthly submissions of all serious cardiorespiratory reactions reportedly associated with use of Versed.[43]

Versed, like Valium, was originally available in a 5 milligram per milliter solution. Roche also acknowledged to the advisory committee on December 1, 1986, that several physicians had reported difficulties titrating the drug at such concentrated levels.[44] Three weeks later, the company submitted a supplemental new drug application for a less concentrated, 1 mg/ml solution of the drug.[45]

In February 1987, Roche issued a "Dear Doctor" letter that, noting reports of Versed-associated respiratory and cardiac arrest, re-emphasized the package insert instructions for safe use of the drug.[46] The letter also recommended an initial titration dose for conscious sedation of 1 to 1.5 mg for older or chronically ill or debilitated patients, which marked a 50 percent reduction from the previously recommended starting dose.[47]

On May 19, 1987, FDA's Anesthetic and Life Support Drugs Advisory Committee again addressed the safety of Versed. By that time, FDA had recorded a total of 30 domestic reports of serious cardiorespiratory reactions for the reporting period from March 1986 through April 1986, 13 of which had been received since December 1, 1986.[48] At the meeting, Roche indicated that it had moved to effect reductions in recommended dosages.[49] In fact, on March 19, 1987, Roche had submitted a supplemental new drug application that called for lowering recommended total conscious se-

[42] See the verbatim transcript of that meeting, page I-79, in subcommittee files. In a similar vein, Dr. Robert M. Julien, Staff Anesthesiologist, St. Vincent Hospital and Medical Center, Portland, Oregon, testified before the subcommittee that at his institution "we have had at least six, perhaps many more very close near misses. . . . We have been, frankly, lucky that we have not had several deaths at our hospital." May 5 Hearing, galley page 6.

[43] The December 16, 1986, letter to Roche from Dr. Janet Arrowsmith, FDA's Office of Epidemiology and Biostatistics, is in subcommittee files.

[44] See page I-77 of the verbatim transcript of the December 1, 1986, meeting of FDA's Anesthetic and Life Support Drugs Advisory Committee, which is in subcommittee files.

[45] Roche's December 22, 1986, supplemental new drug application is in Hearings, Appendix I.

[46] This letter is in Hearings, Appendix I.

[47] At an October 18, 1986, meeting, one anesthesiologist serving on Roche's advisory board for Versed, recommended to Roche representatives that elderly patients receive Versed in "no more than half milligram increments" given over 2- to 3-minute periods. See the transcript of that meeting, Hearings, Appendix I. A published letter to the *British Dental Journal* in 1985 similarly stated: "Because midazolam exhibits such high potency when it is administered intravenously, it is necessary to titrate small incremental doses of *0.5* mg. against the clinical response obtained in the patient." (Emphasis supplied) See Harris, "Midazolam in Dentistry," *British Dental Journal*, 158: 158, 1985. In a similar vein, Dr. Sidney M. Wolfe, Director, Public Citizen Health Research Group, similarly testified that he knew "of gastroenterologists . . . who tell me that some people can respond to as little as *half a milligram* or 1 milligram of this drug." (Emphasis supplied.) May 5 Hearing, galley page 32.

[48] See the May 8, 1987, update by Dr. Janet Arrowsmith, FDA's Office of Epidemiology and Biostatistics, in subcommittee files.

[49] See page 41 of the verbatim transcript of the May 19, 1987, advisory committee meeting, which is in subcommittee files.

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dation doses for non-elderly, healthy adults to a maximum of 0.1 mg/kg.[50]

On May 26, 1987, FDA approved this application as well as the December 22, 1986, application to make available a more dilute, 1 mg/ml. solution.[51]

During his appearance before the subcommittee, Dr. Carl Peck, Director, FDA's Center for Drug Evaluation and Research, testified that from late May through mid-June, FDA received reports of serious cardiorespiratory reactions in four "apparently otherwise healthy" patients "in their mid-20's to mid-30's," which "added to our impression that the recommended dose was too high and that more emphasis needed to be placed on appropriate precautions and warnings for resuscitation while using midazolam." [52]

At an August 19, 1987, meeting with Roche, Dr. Robert Temple, then Director of FDA's Office of Drug Research and Review, emphasized that, while only elderly patients initially appeared to be at risk for serious cardiorespiratory reactions to Versed, such reactions had recently been observed in younger patients, and that the number of reported cases had not diminished since the February 1987 "Dear Doctor" letter. Dr. Temple expressed his preference for a boxed warning to draw practitioners' attention to the dangers of respiratory arrest, since they did not appear "to be getting the message."[53] Actually, Dr. David Scally, FDA's medical reviewer for Versed, had recommended discussion of a "possible box warning [in the Versed package insert] to ensure that practitioners use [Versed] according to directions" on November 19, 1986, nine months earlier.[54]

Although admitting that a boxed warning would hurt sales, Roche's Dr. Philip Del Vecchio told FDA at the August 19, 1987, meeting that he was unpersuaded that such a warning would prove effective.[55]

On September 18, 1987, Roche submitted to FDA a draft of a proposed second "Dear Doctor" letter.[56] Suggested revised labeling also contained in that submission did not include a boxed warning, because, as Roche stated at that time, such a warning was not preferable to intensified physician education efforts.[57]

However, at an October 7, 1987, internal meeting, FDA officials resolved to request that Roche include a boxed warning in the Versed package insert.[58] Accordingly, FDA requested, in an October 9, 1987, letter to the company, that the package insert begin

[50] This supplemental new drug application is in Hearings, Appendix 1.

[51] FDA's May 26, 1987, approval letter is in Hearings, Appendix 1. This concentration was first made available to physicians in July 1987.

[52] May 5 Hearing, galley page 48. Two of these patients had received the drug prior to cosmetic surgery, one prior to nasal surgery and one during a tubal ligation.

[53] See the memorandum of this meeting, in subcommittee files.

[54] His November 19, 1986, review is in subcommittee files.

[55] See the memorandum of that meeting, which is in subcommittee files.

[56] See Roche's September 18, 1987, submission, which is in subcommittee files.

[57] Ibid.

[58] See the October 7, 1987, review of proposed labeling by FDA medical officer David Scally, which is in subcommittee files, which references an FDA internal meeting that day at which this resolution was made. According to Dr. Scally, Dr. Robert Temple, then the Director of FDA's Office of Drug Research and Review, "was very persuasive in support of a BOX WARNING" at this meeting.

with such a warning.[59] In late October 1987, Roche acceded to this request.[60]

On October 23, 1987, Roche advised FDA that it considered it essential that the Versed package insert state that "some patients may respond to as little as 1 mg." of Versed and that more than 5 mg. of the drug was not generally necessary for the sedation of non-elderly, healthy adults.[61] In addition, a maximum total conscious sedation dose of 3.5 mg. of Versed would be generally recommended as adequate for elderly patients.[62] Such changes were incorporated, in fact, into the Versed package insert. Roche also informed FDA at this time that future "[p]romotional campaigns will emphasize the potency of Versed relative to diazepam."[63] Accordingly, a "Dear Doctor" letter that was issued the following month opened:

> Versed is a potent sedative agent which has been widely used for conscious sedation. Clinical experience indicates that it may be *three to four times as potent* per mg as diazepam (Valium)." [64] (Emphasis supplied.)

On February 12, 1988, the Public Citizen Health Research Group (HRG) publicly revealed that the agency had originally approved conscious sedation doses for Versed substantially greater than those shown to be effective in published studies and approved in the United Kingdom. HRG also petitioned FDA on this date to contraindicate the drug's use in conscious sedation and in patients over 60.[65]

As of the subcommittee's May 1988 hearings, FDA had processed 70 domestic reports of serious Versed-associated cardiorespiratory reactions, 36 of which involved fatalities.[66] By early July 1988, the total had risen to 80 reports of serious cardiorespiratory reactions, including 43 deaths.[67] By September 15, 1988, FDA had processed 86 reports of serious, Versed-associated cardiorespiratory events, including 46 fatalities.[67a]

[59] In subcommittee files.

[60] According to Dr. David Scally, FDA's medical reviewer for Versed, in late October 1987, Roche agreed to "add a boxed WARNING to the package insert, a request which they had previously opposed." See Dr. Scally's October 27, 1987, memorandum, which is in subcommittee files.

[61] Roche's October 23, 1987, letter to FDA is in subcommittee files.

[62] Ibid.

[63] Ibid.

[64] Hearings, Appendix 1. The letter also emphasized that Roche had recently received reports of serious cardiorespiratory reactions in younger, healthy patients who did not receive other medications and that some major reactions had occurred in patients receiving doses within the recommended dosage range.

[65] HRG's February 12, 1988, petition to FDA is in Hearings, Appendix I.

[66] Dr. Robert Julien, Staff Anesthesiologist, St. Vincent Hospital,. Portland, Oregon, testified that, in view of the seven Versed-associated deaths of which he was aware in Portland alone, he believed that the 36 Versed-associated cardiorespiratory deaths reported to FDA by that time "grossly" understated the number of such fatalities that had occurred in the United States. May 5 Hearing, galley page 7.

[67] See the July 7, 1988, memorandum by Dr. Janet Arrowsmith, Medical Epidemiologist, Epidemiology Branch, FDA's Office of Epidemiology and Biostatistics, which is in subcommittee files. According to the memorandum, Roche submitted four additional reports, including three deaths, but with insufficient information for inclusion in Dr. Arrowsmith's line listings.

[67a] Dr. Janet Arrowsmith of FDA's Office of Epidemiology and Biostatistics conveyed this information to the subcommittee staff during a September 19, 1988, telephone conversation.

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III. Findings and Conclusions

A. The conscious sedation doses originally approved by FDA were excessive

The committee finds that FDA approved conscious sedation doses substantially higher than those shown to be effective in published studies.

Originally, the recommended total dosage for conscious sedation in a healthy, non-elderly adult ranged from 0.1 to 0.15 mg/kg and, if necessary, up to 0.2 mg/kg,[68] notwithstanding that several studies published in the medical literature years before FDA approved Versed in December 1985 revealed such doses to be excessive.

In October 1982, Al-Khudhairi, Whitwam, and McCloy of the Royal Postgraduate Medical School in London reported in a gastroscopy study published in the British literature that 0.1 mg/kg of Versed—the lower end of the originally recommended dose range in the United States—proved excessive for several patients.[69] Moreover, the 0.1 mg/kg dose had only been selected in the first place after a pilot study had shown a 0.15 mg/kg dose—also within the originally approved U.S. dosage range—to have been unacceptably high.[70]

Another gastroscopy study published the following month by the Departments of Anaesthetics, The Queen's University of Belfast, Northern Ireland, and Royal Brisbane Hospital, Brisbane, Queensland, Australia, mentioned that a previous pilot study had "found that midazolam 0.1 mg/kg appeared to be an effective dose for most patients, but they had a tendency to be oversedated and became uncooperative."[71] "For this reason," the authors wrote, "a smaller dose was preferred." The study found that Versed produced adequate sedation at *0.07 mg/kg*.

On August 8, 1983, Whitwam, Al-Khudhairi, and McCloy of London's Royal Postgraduate Medical School published a second gastroscopy study, which this time favorably compared *0.07 mg/kg* of Versed with 0.15 mg/kg of Valium.[72]

Several additional conscious sedation studies involving the Department of Anesthetics, the Queens University of Belfast, Northern Ireland, published in 1982,[73] 1983,[74] and 1984,[75] demonstrated the adequacy of total Versed doses between 0.07 and 0.10 mg/kg. In fact, according to Professor J. W. Dundee of that department, titration and trial and error had originally demonstrated the appropriateness of these doses for conscious sedation.[76]

An American study published by White et al. shortly before the subcommittee's hearings confirmed these earlier findings.[77] In that study, *0.10 mg/kg* of Versed—the lowest dose in the originally recommended U.S. dose range for the drug—oversedated (i.e., put to sleep) *40 percent* of patients and *.15 mg/kg* of Versed—also within the originally approved U.S. dose range—oversedated *75 percent* of patients.[78] The White study also postulated that an optimal dose

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[68] In this regard, the original Versed labeling stated that "[g]enerally *0.1* to *0.15 mg/kg* is adequate, but up to *0.2 mg/kg* may be given." May 10 Hearing, galley page 3. Roche's proposed labeling revision of June 20, 1986, although not altering these total dosage recommendations, did characterize 0.2 mg/kg as a "rare" necessity. This revision is in Hearings, Appendix I.

However, doses were to be reduced 30 percent if the patient was elderly or debilitated and yet another 25 percent to 30 percent if the patient received certain other kinds of drugs, such as narcotics.

[69] Cooperation was lost from four patients for a period. May 10 Hearing, galley page 3. See, Al-Khudhairi, Whitwam, and McCloy, "Midazolam and diazepam for gastroscopy," *Anaesthesia*, 37: 1002, October 1982, which is in Hearings, Appendix I.

[70] Ibid.

[71] See Brophy, Dundee, Heazelwood, Kawar, Varghese and Ward, "Midazolam, a Water-soluble Benzodiazepine, for Gastroscopy" *Anaesthesia and Intensive Care*, 10: 344, November 1982, which is in Hearings, Appendix I.

[72] May 10 Hearing, galley page 4. Whitwam, Al-Khudhairi and McCloy, "Comparison of midazolam and diazepam in doses of comparable potency during gastroscopy," *British Journal of Anaesthesia*, 55: 773, August 8, 1983.

[73] See Dundee, Kawar, Gamble and Brophy, "Midazolam as a Sedative in Endoscopy," *British Journal of Anaesthesia*, 54: 1136, October 1982, which also investigated Versed at 0.07 mg/kg., and which is in Hearings, Appendix I; Kawar, McGimpsey, Gamble, Browne and Dundee, "Midazolam as a Sedative in Dentistry," *British Journal of Anaesthesia*, 54: 1137, October 1982, which studied Versed at 0.10 mg/kg and was included in an annual report to the Versed IND on August 15, 1986, and which is in Hearings, Appendix I.

[74] See McGimpsey, Kawar, Gamble, Browne, and Dundee, "Midazolam in Dentistry," *British Dental Journal*, 155: 47, July 23, 1983, which investigated Versed at 0.10 mg/kg and which is in Hearings, Appendix I. The manuscript of this study, which is dated September 1, 1982, was submitted in an annual report to the Versed IND on August 19, 1983.

[75] Kawar, Porter, Hunter, McLaughlin, Dundee, and Brophy, "Midazolam for upper gastrointestinal endoscopy," *Annals of the Royal College of Surgeons of England*, 66: 283, July 1984, which studied Versed at an average dose of 0.087 mg/kg and which is in Hearings, Appendix I.

[76] May 10 Hearing, galley page 5. During his appearance before the subcommittee, Dr. Carl Peck, Director, FDA's Center for Drug Evaluation and Research, testified that some of the lower dose clinical trial results published prior to FDA approval

> . . . were based on studies in which a single full dosage was given as an initial dosage, after which time an assessment of the effectiveness and toxicity of the drug administration was made. In the NDA that we evaluated and eventually approved, dosage was on a much different basis. It approved dosage on the basis of titration to a clinical endpoint, not a full dosage to 0.1 or 0.15 or 0.2. In the initial labeling we cautioned the physician to use a dosage that was consistent with the identified clinical endpoint and not to blindly give a total dosage.

May 10 Hearing, galley page 7. However, as the subcommittee staff learned, the total dosages used in the U.K. studies had been previously derived from titration and trial and error. May 10 Hearing, galley page 5.

Contrary to the implication of Dr. Peck's testimony, some lower dose published studies involved titration to a clinical endpoint rather than a fixed total dose. For example, the lower dose gastroscopy study published in 1984 by Kawar, Porter, Hunter, McLaughlin, Dundee, and Brophy, supra, primarily involved administration of Versed to the clinical endpoint of ptosis (drooping of the upper eyelid) and dysarthria (imperfect articulation in speech). Elaboration on this point appears in the summary of this study appearing in Roche's August 31, 1988, submission to FDA, which is in subcommittee files. According to this submission, Versed was administered to the clinical endpoint of slurred speech in other lower dose studies completed years before FDA approval, including a cardiac catherisation study by G. Hendrix at a mean dose of 0.06 mg/kg of Versed. In another unpublished gastroscopy study conducted prior to FDA approval that was summarized in Roche's August 31, 1988, submission to FDA, B. L. Dowling, through titration, achieved a satisfactory, albeit unspecified, sedation endpoint in his patients at a mean dose of 0.076 mg/kg of Versed.

Furthermore, notwithstanding Dr. Peck's testimony, the originally approved labeling for Versed, while it recommended titration to the endpoint of slurred speech, did not caution physicians to start with a dose substantially less than the recommended total dose of 0.1 to 0.15 or 0.2 mg/kg for healthy, non-elderly adults. It was not until June 20, 1986, six months after approval, that Roche proposed adding to the Dosage and Administration section of the Versed labeling an instruction to start with a titration dose of 2.5 mg.

[77] See White, Vasconez, Mathes, Way, and Wender, "Comparison of Midazolam and Diazepam for Sedation During Plastic Surgery," *The Journal of Plastic and Reconstructive Surgery*, 81: 703, May 1988, which is in Hearings, Appendix I.

[78] May 5 Hearing, galley page 25. Dr. Carl Peck, Director, FDA's Center for Drug Evaluation and Research, testified that the design of the White study rendered its findings of limited relevance to the manner in which the drug was recommended for use:

> [T]heir paradigm was to give a total dosage over a very rapid infusion, a paradigm which we have never actually sanctioned. We have always recommended that it be given in incremental doses, titrated to a clincial end point and preferably as a slow in-

Continued

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for conscious sedation might be 0.075 mg/kg, which, as Dr. Robert M. Julien, formerly Associate Professor, Departments of Anesthesiology and Pharmacology, Oregon Health Sciences University, noted, "is almost identical" to the 0.07 dose that was demonstrated to be effective "in the European literature in 1983." [79]

Fundamental to the science of pharmacology is the establishment of the lowest effective dose because, as Dr. Robert M. Julien testified before the subcommittee, "[i]f you go to doses higher than [that], which are effective, you increase the likelihood of toxicity." [80] He expressed the judgment that the conscious sedation doses originally approved by FDA violated this pharmacological objective. The 0.07 to 0.10 mg/kg doses suggested as "appropriate" by several studies conducted in the early 1980's, he testified, were "at least 50 percent below that which was promoted in this country." [81] Accordingly, Dr. Julien concluded that the originally approved conscious sedation doses for Versed "were consistent with overdosage rather than with a safe level of conscious sedation," [82] a judgment with which Dr. Alan Lisbon, Assistant Professor of Anesthesia, Harvard Medical School, concurred.[83]

The committee finds it noteworthy that, as Dr. Carl Peck, Director, FDA's Center for Drug Evaluation and Research, acknowledged,[84] in November 1987 Roche finally reduced the total recommended U.S. conscious sedation dose for Versed to *5 mg* [85] or 0.07 mg/kg (for a 70 kg. person), essentially the same dose found to be effective in published studies predating Versed's U.S. approval.[86] However, Roche did not submit any *post-approval* studies substantiating Versed's efficacy *at or below 0.07 mg/kg* to support its new, lower dose range.[87] Studies supporting such efficacy were published in the medical literature and therefore available to FDA *before* it approved the drug for marketing in the United States. The committee, therefore, finds it indefensible that it was not until *November 1987,* almost two years *after* FDA approval, that the generally recommended maximum Versed conscious sedation dose was finally lowered to 0.07 mg/kg.

By November 1987, the Versed labeling also stated that "some patients may respond to as little as 1 mg.," or 0.014 mg/kg for a 70 kg. person, of the drug.[88] That the drug's originally approved labeling recommended a minimum total dose seven times higher (0.10 mg/kg or 7 mg. for a 70 kg. person) than this underscores the excessiveness of that dose.

B. THE ORIGINALLY APPROVED CONSCIOUS SEDATION DOSES UNDERSTATED VERSED'S POTENCY RELATIVE TO VALIUM

The subcommittee's investigation revealed that by mid-1986 Roche regarded Versed as three to four times as potent as injectable Valium. Despite this, Roche did not reduce the recommended doses of Versed at this early stage of the drug's marketing to 1/4 to 1/3 of those recommended for Valium to conform to this assessment of the drug's relative potency.[89] In fact, members of Roche's sales force apparently detailed Versed to physicians as comparably potent to, or only slightly more potent than, Valium.[90] Moreover, the generally recommended dose of 10 mg. of Valium translates to *0.14 mg/kg* for a 70 kg. person, which was *squarely within the recommended dose range for Versed* of 0.10 to 0.15 or 0.2 mg/kg that was in effect *until mid-1987.*

That Versed was recommended for use at doses comparable to those of a drug of 1/4 to 1/3 its potency graphically illustrates the excessiveness of the conscious sedation doses at which it was originally approved.

Versed was not only recommended for use at doses comparable to Valium but was also packaged in the same concentration—namely, 5 milligrams per milliliter. This led the prestigious medical journal, *The Lancet,* to note in a July 16, 1988, editorial that the

> . . . normal adult dose [in the United States] was therefore not dissimilar to that of diazepam (0.14 mg/kg), and the formulation was the same (5 mg/ml). The implication was that the drugs could be used in a similar fashion. . . .[91]

To be certain, U.S. physicians assumed that they could use Versed in the same manner that they had used Valium. For example, in informing Roche of a fatal respiratory reaction to Versed, one physician, after noting Versed patients in other hospitals in his

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fusion with significant periods in between each incremental dose to assess clinical outcome.

May 10 Hearing, galley page 19. As subcommittee Chairman Weiss noted, the published report of the White study

> . . . indicates that Versed was administered over 30 to 90 seconds. That would not be considered to be a rapid bolus injection.

May 10 Hearing, galley page 20.

Furthermore, contrary to Dr. Peck's testimony, when FDA approved Versed, it did not "recommend that it be given in incremental doses." As he acknowledged in his prepared testimony, "editorial revisions" were made in the Versed labeling in June 1986 "to help prevent the possibility of a clinician starting titration with a whole dose of 0.1 to 0.15 milligrams per kilogram rather than titrating the dosage to a desired response. . . . A suggested initial dose, 2 to 2.5 milligrams in an average healthy adult was given for the first time." May 5 Hearing, galley pages 45–6.

[79] May 5 Hearing, galley page 26. See the 1983 study by Whitwam, et al., supra.

[80] May 5 Hearing, galley page 26.

[81] May 5 Hearing, galley page 23.

[82] May 5 Hearing, galley page 26.

[83] May 5 Hearing, galley page 25.

[84] May 10 Hearing, galley page 18.

[85] Roche stated in the November 1987 version of the Versed labeling that a "total dose greater than 5 mg. is not usually necessary to reach the desired endpoint" for conscious sedation in healthy, non-elderly adults. May 5 Hearing, galley page 25.

[86] In this regard, see the testimony of Dr. Alan Lisbon, Assistant Professor of Anesthesia, Harvard Medical School, May 5 Hearing, galley page 25.

[87] See the testimony of Dr. Carl Peck, Director, FDA's Center for Drug Evaluation and Research, May 10 Hearing, galley page 8.

[88] Dr. Robert M. Julien, formerly Associate Professor, Departments of Anesthesiology and Pharmacology, Oregon Health Sciences University, has advised the subcommittee staff that as little as 1 mg. may even be capable of inducing general anesthesia in some patients.

[89] May 10 Hearing, galley page 23. After consulting anesthesiologists advised Roche representatives at an October 18, 1986, that they thought Versed was 3 to 4 times as potent as Valium, one anesthesiologist asked, "Do they [endoscopists] know what that means to reduce the dose [to] one third or one quarter?" to which a Roche employee responded, "We can make it a little bit more clear." Hearings, Appendix 1.

[90] See the testimony of Dr. Michael Morrisey, Westchester Plastic Surgical Associates, Yonkers, New York, May 5 Hearing, galley pages 9 and 20. Dr. Robert M. Julien, staff anesthesiologist, St. Vincent Hospital, Portland, Oregon, testified before the subcommittee: "Some of my colleagues in other specialties such as cardiology and endoscopy, when they believed from the representative that the drug was equal to Valium, they were initially using doses as high as 20 milligrams, which is way above a dose for induction of general anesthesia." May 5 Hearing, galley page 10.

[91] "Midazolam—Is Antagonism Justified?", *The Lancet,* July 16, 1988, page 141.

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area "going into respiratory and cardiac arrest," observed "that because of the similarity of size and total milligrams of dosage of this product and Valium, physicians are prescribing this product as they would Valium."[92] Dr. Joan W. Flacke, a member of FDA's Anesthetic and Life Support Drugs Advisory Committee, similarly remarked at the December 1, 1986, meeting of that committee that "people are used to using [Valium] in this concentration and now you [Roche] have packaged this in the same concentration."[93] Acknowledging Roche's concern that Versed was "being used as a single bolus or as rapid intraveneous administration despite what the package insert says," a company representative at that meeting, Dr. Philip Del Vecchio, stated that

> . . . there is some indication that that may be happening. That may be related to the way that they are used to using Valium. I think it has been more common to use Valium more rapidly for that titration.[94]

Several weeks earlier, at an October 18, 1986, meeting with consulting anesthesiologists, a Roche official acknowledged that endoscopists were using Versed as if it were Valium, and, as a result "we are getting into trouble."[95]

This, as Dr. Laurence R. Dry, editor and publisher, *Attorney's Medical Advisory Letter*, wrote in October 1986, before FDA or Hoffmann-La Roche had publicized the drug's association with life-threatening cases of respiratory arrest, was a prescription for disaster:

> [M]idazolam is 3 to 4 times as potent as Valium but is marketed in the same dilution, 5 mg/ml. This means that each 5 mg. of midazolam is equivalent to 15-20 mg. of Valium and physicians used to using Valium may easily overdose patients with the newer drug. . . . The packaging of the drug in 10 mg. ampules and syringes (equivalent of 30-40 mg. of Valium) by its manufacturer, Roche, was a gross error.[96]

[92] May 5 Hearing, galley page 17.

[93] See page 1-77 of the verbatim transcript of that meeting, which is in subcommittee files.

[94] See page 1-69 of the verbatim transcript of that meeting, which is in subcommittee files.

[95] That official acknowledged that "we're finding that what they're [i.e., endoscopists] doing is . . . trying to mimic their use of Versed as they had with injectable Valium and we're getting into trouble." May 5 Hearing, galley page 18. Another company official noted that "one of the things that I just communicated to the sales force [is] that everybody is into the Valium routine." The transcript of the October 18, 1986, meeting is in Hearings, Appendix I.

When Roche launched Versed, a company told several anesthesiologists on Roche's advisory board on Versed at that October 18, 1986, meeting that

> . . . [o]ne of the foremost things in the back of our mind was that we knew that we had to get the product [Versed] on board and into your [i.e., anesthesiologists'] hands before generic diazepam [i.e., Valium] became a stronghold.

After hearing a tape recording of this statement, some witnesses appearing before the subcommittee speculated that Roche marketed Versed in a manner that minimized differences in packaging and dosing from Valium so as to ease physician conversion from Valium—a familiar drug that had recently gone off patent—to Versed. See the testimony of Dr. Sidney M. Wolfe, Director, Public Citizen Health Research Group, May 5 Hearing, galley page 19; Dr. Michael Morrisey, Westchester Plastic Surgical Associates, Yonkers, New York, Ibid. Dr. Douglas C. Walta, the Gastroenterology Clinic and Providence Hospital, Portland, Oregon, testified that if the company had admitted how potent Versed was, the drug would have presented such a thin safety margin that he would not have converted to it. May 5 Hearing, galley pages 27-8.

[96] He wrote this in the October 1986 issue of the *Attorney's Medical Advisory Letter*. May 5 Hearing, galley page 17.

Versed, Dr. Dry concluded, is "a very dangerous drug if improperly used and improper use is openly invited with current packaging."[97] The "errors" made by Roche, Dr. Dry presciently predicted, "will cost some lives before packaging of the drug is corrected" since "no warning in the package insert can be deemed sufficient to counteract the disasters invited by current packaging of the drug."[98]

1. The Importance of Reliable Total Dosage Recommendations

Roche has argued that package insert instructions for individualized titration to desired sedation levels, not labeled total dosage ranges, should govern proper dosing.[99]

The pharmacological properties of Versed, however, have often prevented physicians, particularly non-anesthesiologists, from recognizing when patients given Versed are already amply sedated and should not be administered additional doses of the drug. These aspects of Versed's action make it imperative that the drug's package insert recommend use of the lowest total doses at which Versed has been generally found to be effective.

As one of Roche's consulting anesthesiologists, Dr. Ronald Miller of the University of California at San Francisco, has observed, a Versed patient can be moving yet be heavily sedated and "one trap a person unaware of [Versed's] pharmacologic properties can fall into is not recognizing that" such a patient can be undergoing "severe respiratory depression."[100] "If one keeps giving more midazolam until the patient does not move or complain," Dr. Miller added, "respiratory depression will ensue, especially if midazolam is combined with a narcotic."[101] Dr. Alan Lisbon, Assistant Professor of Anesthesia, Harvard Medical School, concurred with this assessment, noting during his appearance before the subcommittee that in clinical practice, the failure to differentiate between insufficient and excess sedation among patients receiving Versed could prove dangerous:

> Many times when people are hypoxic or not receiving enough oxygen to their brain, they become agitated. Abso-

[97] May 5 Hearing, galley page 17. Dr. Dry elaborated before the subcommittee:

> Versed was packaged as though it was Valium and it isn't. It's three to four times as strong. When an endoscopist, who is basically unfamiliar with the drug but who has been told it's the greatest thing since white rice decides to use the drug, he is going to look at the package insert, he's going to look at the size of the ampule. . . . The typical modus is to assume that the proper dose is a vial or a predrawn syringe. That's why I said that the packaging invited disaster. It invites you to use one ampule, which is a whopping dose for most people.

May 5 Hearing, galley page 18.

Dr. Douglas Walta, the Gastroenterology Clinic and Providence Hospital, Portland, Oregon, presented similar testimony to the subcommittee: "[O]ne point is the way the dosage vial comes out, in Valium it came out 10 milligrams in one vial. You draw up the 10 milligrams in a syringe, and that's usually the standard dose. When Versed came out, it came in a 10 milligram per vial or syringe. You drew it up in the syringe, 10 milligrams. That is a huge dose now, in retrospect." May 5 Hearing, galley pages 10-11.

[98] May 5 Hearing, galley page 22.

[99] See its April 25, 1988, letter to FDA in response to the Public Citizen Health Research Group petition of February 12, 1988, Hearings, Appendix I.

[100] May 5 Hearing, galley page 29.

[101] See Miller, "Midazolam in Plastic Surgery." in *Midazolam in Clinical Anesthesiology*, ed. by Epstein and Reves, page 12, 1987, in Hearings, Appendix I.

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lutely, at that time, the wrong thing to do is to inject them with more drug.[102]

Dr. Lisbon further testified that a recently published study[103] indicated that use of Versed may obscure serious losses of oxygen because it suppresses some of the clinical responses such as increased breathing that normally signal such trouble.[104]

Prudent, scientifically supportable total dosage recommendations, Dr. Lisbon testified, are important in minimizing the risk that physicians unaware of Versed's pharmacological dynamics will inadvertently oversedate their patients.[105]

Clearly, labeling instructions to titrate Versed to desired sedation levels cannot substitute for total dosage recommendations that are scientifically demonstrated to be excessive.

Moreover, originally recommended total doses, as well as subsequent reductions in such doses, were presumably inserted into the Versed labeling for a purpose—namely, to provide guidance to the practitioner. Even Roche acknowledged that "[d]rug labeling generally provides a dosage range to guide the physician as to how much drug might be needed during the procedure."[106] It is contradictory to disclaim the importance of specific total dosage information that has consistently comprised an integral part of the drug's labeling.

That Versed should be individually titrated to a particular endpoint need not detract from the desirability of providing guidance as to a typically appropriate total dose range. As Dr. Sidney Wolfe, Director, Public Citizen Health Research Group, testified,

> . . . to omit the importance or underemphasize the importance of the range where you are supposed to get going as opposed to the titrating kind of thing, it's just misleading. People need as much information as possible.[107]

The labeling for Versed has steadily advised titration to the clinical endpoint of slurred speech. According to Dr. Alan Libson, Assistant Professor of Anesthesia, Harvard Medical School, this advice is "foolhardy," because at this endpoint,

> . . . there will be a significant amount of respiratory depression and the patient may lose their ability to protect their airway. I think that even those recommendations are excessive.[108]

Even an anesthesiologist on Roche's advisory board for Versed, Dr. Ronald Miller of the University of California at San Francisco, has expressed the opinion that "it seems better not to reach the point of slurred speech, but merely to take the edge off precise speech."[109]

To the extent that slurred speech may have been an inappropriate clinical endpoint, the committee believes it was particularly important that physicians were not misled by recommended total doses shown to be excessive in well-controlled scientific studies.

2. The Role of Medical Mismanagement in Assessing the Safety of Versed

In a May 6, 1988, letter to the subcommittee, Dr. Donald R. Stanski, Associate Professor of Anesthesia and Medicine at the Stanford University School of Medicine, echoed a theme that permeates FDA's post-market consideration of the safety of Versed—namely, that physicians failing to recognize and treat respiratory depression, not Versed, were responsible for subsequent respiratory arrest and death.[110] To be certain, many Versed-associated deaths appear to have resulted, at least in part, from medical mismanagement of patients experiencing life-threatening respiratory depression. As Dr. Laurence Dry, editor and publisher, *Attorney's Medical Advisory Letter,* has noted,

> Supportive treatment is required until the drug is "worn-off"—the patient's airway must be controlled and his ventilation assisted. This is particularly important when the drug is given in the endoscopy suite for bronchoscopy or gastroscopy. Here, . . . monitoring equipment is not frequently used, and abilities of personnel to recognize respiratory depression and treat it may not be sufficient.[111]

By the nature of their tasks, endoscopists must concentrate on performing the endoscopy rather than observing the patient. Anesthesiologists, who focus their full attention on monitoring patient response to drugs like Versed[112] and are often more cautious in

[102] May 5 Hearing, galley page 29. One published study similarly observed:

> In addition, we were impressed by the close temporal relationship between the onset of gagging, coughing/choking and a fall in oxygen saturation. It would be tempting to administer further intravenous sedation to such patients, thereby further depressing ventilation, with potentially disastrous consequences.

Bell, Reeve, Moshiri, Morden, Coady, Stapleten & Logan, "Intravenous midazolam: A study of the degree of oxygen desaturation occurring during upper gastrointestinal endoscopy," *British Journal of Clinical Pharmacology,* 23: 703, June 1987.

[103] See Alexander and Gross, "Sedative Doses of Midazolam Depress Hypoxic Ventilatory Responses in Human," *Anesthesia and Analgesia,* 67: 377, February 1988, which is in Hearings, Appendix I.

[104] May 5 Hearing, galley page 29. He testified that

> . . . if you make some people hypoxic or you deprive them of oxygen, then there are various physiological responses that people have. A drug like midazolam—and there are papers that show this particularly about midazolam—blunts these kind of responses that people in endoscopy for example, are used to looking for. When most people become hypoxic or they are deprived of oxygen, their pulse rate goes up. There are studies in the literature that show if you have given these people midazolam, then their pulse rates don't go up, as you would expect them to do.

May 5 Hearing, galley page 22.

[105] May 5 Hearing, galley page 29. In this connection, he testified that the likelihood that many physicians, particularly endoscopists, administering Versed will not realize that their patients are already sedated and do not need more of the drug enhances the importance of recommending the lowest effective doses. Ibid.

[106] See Roche's April 25, 1988, letter to FDA in response to the February 12, 1988, petition concerning Versed from the Public Citizen Health Research Group, Hearings, Appendix I.

[107] May 5 Hearing, galley page 32.

[108] May 5 Hearing, galley page 28.

[109] He wrote this in a paper presented at a February 1986 Roche-sponsored conference in Phoenix. May 5 Hearing, galley page 28.

[110] Records furnished to the subcommittee following its May 1988 hearings on Versed indicate that Dr. Stanski was at the time he wrote this letter a paid consultant to FDA. FDA reimbursed Dr. Stanski and a colleague for a three-day stay in the Washington, D.C. area. Dr. Stanski also received an honorarium for presenting a seminar to the Center for Drug Evaluation and Research scientific staff on "Pharmacokinetics of "Versed" in the Elderly.

[111] See the October 1986 issue of the *Attorney's Medical Advisory Letter,* in Hearings, Appendix I. In fact, as Dr. Dry testified before the subcommittee, in endoscopy settings "[t]he people that are giving the drug are typically not physicians. They are either untrained technicians or nurses." May 5 Hearing, galley page 22.

[112] One anesthesiologist advised Roche representatives at an October 18, 1986, meeting:

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administering such drugs [113] and more experienced in dealing with respiratory depression,[114] are rarely present during such procedures.

That death and other severely adverse outcomes may ultimately result from inadequate recognition and treatment of respiratory distress, however, certainly *does not justify excessive dosage recommendations that may have unnecessarily contributed to such distress in the first instance.* To the contrary, the failure of some endoscopists to administer Versed properly or to recognize and adequately treat patients experiencing respiratory depression enhances rather than diminishes the case for recommended doses that are not excessive. Endoscopists, if anything, need a drug with a wide margin between effective and toxic doses.

Patient mismanagement *after* drug-induced respiratory depression occurs, while it may have contributed to an adverse outcome, does not exonerate the drug as the initial cause of the toxic reaction. To the extent that patient monitoring capabilities are known to be inadequate in endoscopy settings, the committee believes that problems with an exceptionally potent drug such as Versed were foreseeable.

At the December 1, 1986, meeting of FDA's Anesthetic and Life Support Drugs Advisory Committee, Dr. David L. Scally, FDA' s medical reviewer for Versed, stated that practitioners "may have used diazepam without the same sort of problems that they are getting into with midazolam." [115] That Versed is capable of inducing serious, even life-threatening respiratory depression at substantially lower doses than Valium may be germain to evaluating the safety of its use in the endoscopy setting.

The committee notes, in fact, that the Public Citizen Health Research Group has petitioned FDA to contraindicate Versed's use for conscious sedation precisely because of the increased likelihood

> . . . [W]e're monitoring the hell out of the patients now, particularly the elderly patients and the patients with conscious sedation who are having regional anesthesia, and we're seeing with pulse oximeters fairly major drops in oxygen saturation . . . and it's as far as I can tell, it was rectified with some oxygenation, but you can't get the endoscopists to do anything like that.

See the transcript of this meeting, Hearings, Appendix I.

[113] At an October 18, 1986, meeting with consulting anesthesiologists, a Roche representative stated that "[o]ur problem is with the endoscopists. . . . [b]ecause what's happening out there is they seem to be giving too much too quickly." In response, one of the consulting anesthesiologists observed that "anesthesiologists are used to titrating drugs, and the endoscopists get fixed combinations." Another anesthesiologist noted that "their [endoscopists'] problem with oversedation" is "probably mostly due to the lack of patience on their part in waiting for the desired effect to take place." Along similar lines, another anesthesiologist advised Roche representatives at this meeting that:

> . . . the endoscopists that I've spoke to that were going back to Valium have said that they're happy with Valium. What the hell do they need this drug for? . . . [I]f you want to take the time to inject the dose in a proper manner which we can give you a formula for, then they want to know why they should bother.

The transcript of the October 18, 1986, meeting appears in Hearings Appendix I.

[114] Anesthesiologists are more accustomed to dealing with respiratory depression, inasmuch as they seek to produce underventilation when they use larger doses of a drug like Versed to induce general anesthesia. By contrast, endoscopists would view respiratory depression as an untoward side effect of such a drug. See the June 1, 1988, letter to Rep. Jim Lightfoot from Dr. Stanley B. Benjamin, Chief, Division of Gastroenterology, Department of Medicine, Georgetown University Hospital, in Hearings, Appendix II.

[115] See the verbatim transcript of that meeting, page 1-63, in subcommittee files. At that same meeting, Dr. Philip Del Vecchio of Hoffmann-La Roche stated: "In regard to Valium, I don't have the details on when Valium was first marketed intravenously but I know that the reports were much less than this." Ibid, page I-74.

of patient mismanagement in this setting. Similarly, several witnesses appearing before the subcommittee testified that use of Versed had been limited to anesthesiologists in their institutions,[116] a circumstance that generally all but precludes the drug's use for endoscopies.[117] France, in fact, has limited promotion and use of the drug to anesthesiologists.[118] While the committee takes no position on the safety of Versed for use by non-anesthesiologists, it believes that the likelihood of medical mismanagement cannot be divorced from the question of whether the drug is appropriately indicated for this purpose.

C. FDA WAS UNAWARE OF STUDIES DEMONSTRATING THE EFFICACY OF VERSED AT DOSES LOWER THAN IT ORIGINALLY APPROVED

Some of the previously discussed studies suggesting the efficacy of Versed at total doses as low as 0.07 mg/kg were completed prior to the December 16, 1982, submission of the Versed NDA. For example, a paper on the study by Whitwam et al. was presented at a March 1982 meeting of the British Society of Gastroenterologists.[119]

However, Dr. David L. Scally, FDA's medical reviewer for Versed, testified before the subcommittee that he "did not see any mention" made of these lower, effective doses for conscious sedation in the NDA that Roche submitted to FDA on December 15, 1982.[120] Nor did FDA review any of these studies prior to approving Versed in December 1985.[121] In fact, neither Dr. Scally [122] nor

[116] Dr. Douglas C. Walta, Gastroenterology Clinic and Providence Hospital, Portland, Oregon, testified that "[i]n our facility, Versed is used only by the anesthesiologist." May 5 Hearing, galley page 7. Dr. Michael Morrisey, Westchester Plastic Surgical Associates, Yonkers, New York, similarily testified that Versed is used only by anesthesiologists in the three hospitals in which he works. May 5 Hearing, galley page 8. Dr. Alan Lisbon, Assistant Professor of Anesthesia, Harvard Medical School, and Co-Chairman, Respiratory-Surgical Intensive Care Unit, Beth Israel Hospital, Boston, Massachusetts, testified that with very few exceptions endoscopists at Beth Israel do not use Versed. May 5 Hearing, galley page 23.

[117] Dr. Robert Julien, staff anesthesiologist, St. Vincent Hospital, Portland, Oregon, remarked before the subcommittee that the U.S. lacks the manpower and funding through Medicare and other sources to support use of anesthesiologists in endoscopies. May 5 Hearing, galley page 23.

[118] On July 7, 1987, based on worldwide reports of respiratory insufficiency, France recommended that Versed only be administered by anesthesiologists and, since then, Roche has limited promotion of the drug in France to anesthesiologists. May 10 Hearing, galley page 28. Since Roche did not report these developments to FDA, FDA did not find out about them until it received a December 18, 1987, letter from the French regulatory authority. May 10 Hearing, galley page 28.

[119] May 10 Hearing, galley pages 4-5.

[120] May 10 Hearing, galley page 5.

[121] See the testimony of Dr. David L. Scally, FDA's medical reviewer for Versed, Ibid.

[122] May 10 Hearing, galley pages 5-6. As late as the December 1, 1986, meeting of FDA's Anesthetic and Life Support Drugs Advisory Committee meeting on Versed, Dr. Scally did not question the recommendation that Versed be administered at doses comparable to those recommended for Valium, noting that in the Valium vs. Versed studies, the "dosage came out the same." See page 1-81 of the verbatim transcript of that meeting, which is in subcommittee files.

In a June 23, 1988, memorandum, which is in subcommittee files, Dr. Scally, acknowledging that the "amount of drug initially prepared now seems large," wrote:

> [T]he preparation of equal doses of midazolam and diazepam could have affected dosage results by suggesting to the persons administering the drugs that the dose of midazolam would be close to the dose of diazepam, then a more familiar drug. . . . During clinical investigation of i.v. midazolam and diazepam for the production of conscious sedation, the ratio of the mean midazolam/mean diazepam dose varied between 0.757 (75.7%) and 0.897 (89.7%), depending on the age group selected and whether or not the protocol included use of a narcotic. This would suggest that the average dose of midazolam would be approximately 4/5 the customary dose of diazepam. I hope that my retrospective analysis includes valid reasons why this ratio may not be correct.

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any FDA representative appearing before the subcommittee on May 10, 1988, was aware of any of these studies prior to FDA approval.[123]

1. FDA Did Not Familiarize Itself With Important Papers in the World Literature Prior To Approving Versed

That FDA did not know about several studies suggesting that the originally approved conscious sedation dose range of 0.1 to 0.2 mg/kg for Versed was too high evidences the agency's lack of awareness of important papers on Versed in the world literature.

The subcommittee's investigation also revealed that a Swedish gastroscopy study published by Berggren et al. in Britain in April 1983, more than *two years before Versed was approved* for U.S. marketing, suggested that Versed was *3 times as potent* as Valium.[124] Accordingly, the Versed dose used was *three times smaller* than the Valium dose to which it was compared; the study generally contrasted *0.05 mg/kg* of Versed with *.15 mg/kg* of Valium and found them both to produce adequate sedation.[125]

Roche did not submit the Berggren study to FDA [126] and only first mentioned its existence in an April 25, 1988, submission to the agency, and when FDA approved Versed for conscious sedation at 0.1 to 0.2 mg/kg, FDA was not aware that the drug could be considered three to four times as potent as injectable Valium. Indeed, as earlier discussed, the doses it originally sanctioned for the drug assumed that it was of comparable potency to Valium. In fact, as late as the subcommittee's May 10, 1988, hearing, FDA witnesses testified that they were not familiar with the Berggren study.[127]

This is not the first case in which the committee has found FDA uninformed about major papers in the published medical literature. For example, last year we concluded that FDA's regulation of the antidepressant, Merital (nomifensive maleate), did not reflect review of important articles in the world literature and, accordingly, we recommended that FDA adopt measures to ensure "timely receipt and review of all important publications in the world literature pertinent to evaluating the safety and efficacy of a new drug under review." [128] The committee further recommended that FDA, prior to approving a new drug, "require its scientists to review" a compilation of the world literature concerning that drug provided by the computerized Medical Literature Analysis and Retrieval System (MEDLARS) maintained by the National Library of Medicine.[129] To date, FDA has failed to implement this recommendation.[130]

[123] May 10 Hearing, galley pages 5-6.

[124] May 10 Hearing, galley pages 24-5. See Berggren, Eriksson, Mollenholt and Wickbom, "Sedation for Fibreoptic Gastroscopy: A Comparative Study of Midazolam and Diazepam," *British Journal of Anaesthesia*, 55: 289, April 1983, which is in Hearings, Appendix I. A previous pilot study discussed in this paper yielded that conclusion. In an April 25, 1988, submission to FDA, Roche cited a 1982 publication for what appears to be the same work of Berggren et al. May 10 Hearing, galley page 25.

[125] Ibid.

[126] See Roche's August 12, 1988, submission to FDA, which is in subcommittee files. FDA has advised the subcommittee that "[w]e have no record of the Berggren study being submitted to the Food and Drug Administration." Hearings, Appendix I.

[127] May 10 Hearing, galley page 25.

[128] May 10 Hearing, galley page 6.

During his appearance before the subcommittee, the Director of FDA's Center for Drug Evaluation and Research, Dr. Carl Peck, when asked what steps FDA had taken to adopt committee recommendations aimed at ensuring agency review of important publications in the medical literature, testified that in 1985 FDA promulgated new regulations requiring a "brief description of the marketing history" of any new drug covered by "any NDA submitted after that date." [131] Nothing in this regulation, however, guarantees agency review of all important publications regarding such a drug. Yet, Dr. Peck acknowledged to the subcommittee that "[w]e should be aware of and we should be in a position to take into account information available in the world literature on the subject drug." [132] The committee agrees, and hopes that FDA will take steps to obtain and review all publications in the world literature that are relevant to a responsible assessment of the conditions under which a new drug may be safely and effectively used.

2. FDA Did Not Review All Significant Information in Its Files Concerning Versed Prior To Approving the Drug

Some of the previously discussed lower dose studies concerning Versed had actually been reported to the agency. For example, the manuscript of the study by Al-Khudhairi et al. that was published in October 1982 was submitted to the Versed IND on August 19, 1983.[133] Similarly, a manuscript of the study by Whitwam et al. was reported to the Versed IND on August 24, 1984.[134]

That FDA approved Versed without knowing about such studies indicates that the agency was oblivious to information that had been reported to the Versed IND. In 1983, the committee likewise found that FDA approved the anti-arthritis drug, Oraflex (benoxaprofen), in ignorance of relevant safety information that had been reported to the Oraflex IND. The committee recommended that, prior to approving a new drug, FDA establish procedures to ensure review of all files that might contain potentially important information concerning it.[135]

None of the previously discussed lower dose studies, including those reported to the Versed IND, was ever submitted to the Versed NDA file.[136] Yet, as FDA medical reviewer, Dr. David Scally, testified, once an NDA is filed, most agency attention is focused on the NDA rather than its companion IND file.[137] In view

[129] See *FDA's Regulation of the New Drug Merital*, H. Rep. 100-206, Fifteenth Report by the Committee on Government Operations, July 8, 1987, page 94.

[130] Ibid., page 41.

[131] May 10 Hearing, galley page 6.

[132] May 10 Hearing, galley page 7.

[133] On August 19, 1983, Roche included a January 19, 1982, manuscript of this study in an annual report to the Versed IND. May 10 Hearing, galley page 4.

[134] May 10 Hearing, galley page 4. Roche included a manuscript of this study in an annual report to the Versed IND. Ibid.

[135] See *Deficiencies in FDA's Regulation of the New Drug "Oraflex"*, House Rep. No. 98-511, Fourteenth Report by the Committee on Government Operations, 98th Cong., 1st Sess., November 9, 1983, page 8.

[136] May 10 Hearing, galley page 4.

[137] May 10 Hearing, galley page 4. Similarly, FDA testified before the subcommittee in 1982: "After the NDA is filed, the primary attention of the reviewers is on the NDA and not the IND."

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of this state of affairs, the committee believes that consideration should be given to consolidating the NDA and IND files for all information submitted to the agency in connection with the safety and efficacy of a new drug for which a new drug application has been submitted.

At the very least, as subcommittee Chairman Weiss noted, it makes sense to "have someone looking at the IND submissions as well to evaluate their impact on the decisions being made," an observation with which Dr. Carl Peck, Director, FDA's Center for Drug Evaluation and Research, agreed.[138] Should FDA continue to permit sponsors to submit potentially important information regarding a new drug under NDA review only to the companion IND file for the drug, the committee believes that the agency should take steps to assure a thorough examination of all IND submissions that might contain such information.

D. FDA WAS NOT AWARE OF THE MANNER IN WHICH VERSED WAS REGULATED IN FOREIGN NATIONS

1. Foreign Labeling

FDA officials learned for the first time at the subcommittee's May 10, 1988, hearing that United Kingdom regulatory authorities relied on eventually published studies in approving conscious sedation doses for the drug.[139] In this connection, on April 20, 1988, Professor J. G. Whitwam of the Royal Postgraduate Medical School in London informed the subcommittee staff that the U.K. Committee on Safety of Medicines primarily drew from his and his colleagues' work[140] and investigations by the Queens University of Belfast, Northern Ireland, for the conscious sedation doses that were recommended in the British labeling.[141] In an April 28, 1988, telephone conversation with the subcommittee staff, Professor J. W. Dundee of the Department of Anesthetics, the Queens University of Belfast, Northern Ireland, confirmed this.[142] At the time of U.K. approval of Versed, Professor Dundee reviewed anesthetic and sedative drugs for the Committee on Safety of Medicines, the U.K.'s FDA equivalent.[143]

That is the primary document." See Hearings before a Subcommittee of the Committee on Government Operations, "The Regulation of New Drugs by the Food and Drug Administration: The New Drug Review Process," August 3 and 4, 1982, page 120.

[138] May 10 Hearing, galley page 8.

[139] See the testimony of Dr. David L. Scally, FDA's medical reviewer for Versed, May 10 Hearing, galley page 5.

[140] The study by Whitwam et al., supra, published in August 1983 was actually completed before Versed was marketed in the United Kingdom in January 1983. May 10 Hearing, galley pages 4-5. Dr. Whitwam was also one of the co-authors of the study by Al Khudhairi, et al. published in October 1982.

In an April 29, 1988, letter to the subcommittee, Dr. Whitwam, referring to these two studies, stated that they constituted "the data from which formed a substantial part of the submission to the Committee on the Safety of Medicines in the U.K." In subcommittee files.

[141] May 10 Hearing, galley page 5.

[142] Ibid. In an October 1984 review article, Dr. Dundee summarized previously conducted studies and concluded: "Dosage should be titrated according to patient response; but as a guide, midazolam 0.07 to 0.1 mg/kg is usually given for intravenous sedation . . ." Dundee, et al. "Midazolam: A Review of its Pharmacological Properties and Therapeutic Use," *Drugs*, 28: 519, 1984.

[143] May 10 Hearing, galley page 5.

Months after the subcommittee's hearings, Hoffmann-La Roche itself confirmed that four studies involving Whitwam,[144] Dundee,[145] and their respective associates were among the 14 study report summaries submitted to British regulatory authorities for U.K. marketing approval.[146] Also included among these summaries were reports on other sedation studies demonstrating the efficacy of Versed at doses less than 0.1 mg/kg.[147]

Consistent with the clinical findings of studies conducted prior to the U.K. approval of Versed, the original British labeling for the drug dated December 1982 stated: "As a guide, *0.07 mg/kg* bodyweight has been shown to be adequate in most cases."[148] (Emphasis supplied.) The committee finds it remarkable that it was not until November 1987—almost *five years later* and two years after Versed was approved for U.S. marketing that the generally recommended conscious sedation dose in the U.S. package insert was reduced to approximately this level.

Unbeknownst to FDA, the Swedish study by Berggren et al. that was published in the British literature in April 1983 suggested that a Versed dose as low as *0.05 mg/kg* could be adequate for conscious sedation.[149] Perhaps not coincidentally, at least five countries—Switzerland,[150] West Germany,[151] Sweden,[152] Norway,[153] and the Netherlands[154]—had approved Versed for conscious sedation at a recommended dosage range of *0.05* to 0.10 mg/kg well *before* FDA approval. The West German label even warned that "doses higher than 0.1 mg/kg of body weight may produce oversedation. . . ."[155]

[144] Roche's August 31, 1988, submission to FDA, which is in subcommittee files, stated that the following two study reports were included in the British marketing application as summaries: Al-Khudhairi, Whitwam, and McCloy, "Midazolam and Diazepam for Gastroscopy," supra; and Whitwam, Al-Khudhairi, and McCloy, "Comparison of Midazolam and Diazepam in Doses of Comparable Potency During Gastroscopy," supra.

[145] In an August 31, 1988, submission to FDA, which is in subcommittee files, Roche stated that the following studies were included in the British marketing application as summaries: Kawar, Porter, Hunter, McLaughlin, Dundee, and Brophy, "Midazolam for upper gastrointestinal endoscopy," supra; Dundee, Kawar, Gamble and Brophy, "Midazolam as a Sedative in Endoscopy," supra.

[146] In a June 2, 1988, letter to Roche, which is in subcommittee files, Dr. Philip G. Walters, Acting Director, Division of Surgical-Dental Drug Products, Office of Drug Evaluation I, requested reports of studies "submitted to the regulatory agency in England to support approval of midazolam for conscious sedation." Roche responded with an August 31, 1988, submission, which is in subcommittee files.

[147] See, for example, a gastroscopy study by B.L. Dowling at a mean dose of 0.076 of Versed, and a cardiac catherisation study by G. Hendrix at a mean dose of 0.06 mg/kg of Versed. These studies are summarized in Roche's August 31, 1988, submission to FDA, which is in subcommittee files. The work of Hendrix was eventually published. See Hendrix and Usher, "A comparison of midazolam and diazepam for sedation during cardiac catheterization." *Clin. Res. Abs.*, 31: 706A, 1983.

[148] May 10 Hearing, galley page 9.

[149] See Berggren et al., supra.

[150] May 10 Hearing, galley page 9.

[151] Ibid.

[152] Ibid.

[153] See Roche's August 31, 1988, submission to FDA, which is in subcommittee files. In a September 30, 1986, submission to FDA, which is in subcommittee files, Roche stated that Versed was initially marketed in Norway on May 1, 1985.

[154] See Roche's August 31, 1988, submission to FDA, which is in subcommittee files. In a September 30, 1986, submission to FDA, which is in subcommittee files, Roche stated that Versed was initially marketed in the Netherlands on August 1, 1984.

[155] May 10 Hearing, galley page 9. Such a warning was consistent with the October 1982 gastroscopy study published by Al-Khudhairi et al. in which 0.1 mg/kg of Versed had proven excessive for four patients from whom cooperation was lost for a period. See Al-Khudhairi et al., supra.

In an unpublished Roche internal research report dated December 16, 1982, entitled, "Study of the efficacy and safety of midazolam i.v. administered to patients undergoing bronchoscopy,"

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In addition, since December 1982, the British labeling prominently stated: "THE *ELDERLY* ARE MORE SENSITIVE TO THE EFFECTS OF BENZODIAZEPINES AND IN THESE PATIENTS THE LOWER DOSE OF *2.5 MG.* [.036 MG/KG FOR A 70 KG. PERSON] MAY BE ADEQUATE."[156] (Emphasis supplied.) By contrast, FDA originally approved labeling recommending conscious sedation doses from 5 to 10 mg. (or 0.07 to 0.14 mg/kg) for a 70 kg. elderly patient,[157] two to four times higher than those recommended years before in the United Kingdom.

Dr. David L. Scally, FDA's medical reviewer for Versed, testified that, to his knowledge, not only did Hoffmann-La Roche fail to inform FDA of the lower foreign dosage recommendations before the drug was approved for U.S. marketing,[158] but also that he did not know about them prior to approval.[159] In fact, it was not until after FDA received the February 12, 1988, petition from the Public Citizen Health Research Group that discussed the lower Versed doses recommended in the United Kingdom before FDA approval that the agency requested from Roche all foreign labeling in effect for the drug.[160]

Last year, the committee found that FDA had not informed itself of important aspects of the manner in which the antidepressant, Merital, had been labeled in other nations. Accordingly, we recommended that the agency require all sponsors to submit to it "all labeling approved by foreign regulatory agencies."[161] On the basis of the Versed case, the committee must reiterate this recommendation.

2. Important Foreign Regulatory Developments

Prior to approving Versed, FDA was not informed of important events surrounding regulation of the drug outside the United States. Particularly noteworthy was the agency's lack of awareness of actions taken in the United Kingdom to minimize the risk of Versed-associated respiratory depression.

From January 1983 until early 1985, the concentration of the intravenous solution of Versed permitted in the United Kingdom was 5 milligrams per milliliter,[162] the same as that originally approved in the United States. A letter published in the *British Dental Journal* in April 1984, more than *20 months before FDA approved the drug,* stated that Versed "is at least two or three times as potent as [Valium] and is therefore hard to titrate against patients' response in such a relatively concentrated form" and should probably "be available in a *more dilute form.*"[163] (Emphasis supplied.) In a letter to the same journal the following month, another U.K. practitioner similarly wrote:

> I have had some experience in the intravenous use of both diazepam and midazolam and there is no doubt that the latter is far too concentrated to allow careful titration against the patient. There is a real need for the manufacturers to present the drug in a more dilute form.[164]

Responding to the first letter discussed in the previous paragraph, the *head of medical affairs of Roche's U.K. affiliate* acknowledged in May 1984, *more than 1½ years before FDA approval,* that with Versed "it need not be difficult to oversedate the patient" and that Roche was "looking to see whether further benefits could ensue from a more dilute solution being made available" in the United Kingdom.[165]

On February 4, 1985, several months before FDA approval of Versed, a more dilute *10 milligram per 5 milliliter* solution was introduced in the U.K.[166] This represented a *reduction* in concentra-

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Dr. R. Keller, Chief of Staff, Pneumological Department, Canton Hospital of Aarau, found that patients given approximately *0.1 mg/kg* of Versed during a bronchoscopy developed serious respiratory disturbances, including acute hypoxemia and brief apnea and that "simultaneous administration of oxygen is necessary to avoid hypoxic crises." The subcommittee staff found no FDA reviews of this study, which was buried in a multi-volume annual report to the Versed IND made on August 24, 1984. Although the study was uncontrolled and involved small numbers of patients, its recommendation for supplemental oxygen was reiterated years later in a published report that the administration of nasal oxygen prevented hypoxaemia during gastrointestinal endoscopy. See Bell, Bown, Morden, Coady, Logan, "Prevention of Hypoxaemia During Upper-Gastrointestinal Endoscopy by Means of Oxygen Via Nasal Cannulae," *The Lancet,* 1940: 1022, May 2, 1987. In the report of another study, Dr. Bell and associates wrote:

> It was of considerable concern to us that 7% of our patients desaturated to below 80% during the endoscopic procedure, since cardiac arrhythmias are particularly liable to occur at times of hypoxaemia.

Bell, Reeve, Moshiri, Morden, Coady, Stapleten & Logan, "Intravenous midazolam: A study of the degree of oxygen desaturation occurring during upper gastrointestinal endoscopy." *British Journal of Clinical Pharmacology,* 23: 703, June 1987.

[156] May 10 Hearing, galley page 8 and Hearings, Appendix I. In fact, in 1984, Roche's U.K. affiliate defended a case involving Versed's use in the death of a *76-year-old* endoscopy patient who had been given *10 mg.* of Versed on the grounds that 10 mg. was a "dose 4 times higher than the recommended dose [i.e., of *2.5 mg.*] recommended for a person of his age." May 10 Hearing, galley pages 8-9. This observation, which emphasized the British labeling's *2.5 mg.* total dosage recommendation for *elderly* patients, was not included when Roche reported the case to FDA on July 26, 1985, as one line in a printout of several cases. May 10 Hearing, galley page 9.

According to Roche, this recommendation was based on the "1980 policy of the U.K. Committee on the Review of Medicines that the recommended dosing instructions for *any* benzodiazepine be reduced by 50% in elderly patients." See footnote 7 of Roche's April 25, 1988, response to the February 12, 1988, petition concerning Versed from the Public Citizen Health Research Group, Hearings, Appendix I.

[157] These doses reflect the 30 percent reductions from suggested doses for younger, healthy adults that were recommended for elderly patients in the originally approved labeling for Versed.

[158] May 10 Hearing, galley page 9.

[159] Ibid.

[160] In a March 7, 1988, letter, Dr. Paula Botstein requested all such foreign labeling from Roche. In subcommittee files.

[161] May 10 Hearing, galley page 9.

[162] May 10 Hearing, galley pages 25-6. At the time, Versed was marketed in the U.K. as a *10 mg/2 ml.* solution, which was the same as that approved in the U.S. This concentration translates to 5 mg. of drug for each ml. of solution.

[163] May 10 Hearing, galley page 25. C. M. Hill wrote this in the April 7, 1984, *British Dental Journal.*

Roche submitted this published letter to FDA on August 15, 1986, almost eight months *after* approval, as part of an annual report to the Versed IND. FDA was apparently unaware of this letter prior to approving Versed. FDA's medical officer for Versed, Dr. David L. Scally, testified at the subcommittee's May 10, 1988, hearing that he only "[r]ecently" learned of this letter. May 10 Hearing, galley page 25.

[164] See the letter by B. Royston Sillers in the May 19, 1984, *British Dental Journal,* May 10 Hearing, galley page 25 and Hearings, Appendix I. Another letter to the *British Dental Journal* appearing the following year similarly stated:

> Because midazolam exhibits such high potency when it is administered intravenously, it is necessary to titrate small incremental doses of 0.5 mg against the clinical response obtained in the patient. Such amounts are difficult to dispense accurately from a 2 ml solution containing 10 mg midazolam.

See Harris, "Midazolam in Dentistry," *British Dental Journal,* 158: 158, 1985.

[165] May 10, Hearing, galley page 26. P. A. Harris, head of medical affairs, Roche Products Ltd., wrote this in the May 19, 1984, issue of the *British Dental Journal.*

[166] May 10 hearing, galley page 26.

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tion from 5 mg. of drug in 1 ml. of solution to *2 mg. of drug in 1 ml.* of solution.

Around this time, the U.K. regulatory authority circulated to physicians throughout the United Kingdom a publication "alerting them to the problems which had been reported of respiratory depression with this drug."[167] After discussing seven reports of respiratory depression, including two deaths, the publication concluded:

> An additional preparation of [Versed], containing 10 mg in 5 mil., is to be made available to *enable easier individual titration of dosages. . . . It is hoped that [this measure] will prevent further cases of respiratory depression with this drug. . . .* [168] (Emphasis supplied.)

Roche did not report this publication to FDA prior to the drug's approval,[169] or, for that matter, that the concentration of the drug had been reduced in the United Kingdom in order to minimize the risk of oversedation and serious respiratory depression.[170] Nor did FDA learn that years before Versed was approved, prominent American anesthesiologists advising Roche, including several Versed clinical investigators, urged the company to market a more dilute solution to protect against oversedation, particularly by endoscopists unable to dilute it.[171]

Not surprisingly, prior to approving Versed, FDA did not learn of the changes made in the concentration of the intravenous solution of the drug in the United Kingdom. In fact, during his appearance before the subcommittee, FDA medical officer, Dr. David Scally, testified that he still did not know when a more dilute solution became available in the United Kingdom.[172]

Judging from the post-market history of Versed in the United States, FDA would clearly have benefited from pre-approval knowledge of events surrounding changes in the drug's concentration in the U.K., since once Versed was introduced to the American market, U.S. physicians experienced the same difficulties in titrating the drug and its highly concentrated, 5 mg/ml. solution as did their British counterparts prior to February 1985. At a December 1, 1986, meeting of FDA's Anesthetic and Life Support Drugs Advisory Committee, for example, a Roche official acknowledged that physicians had been complaining that they "had difficulty titrating" the 5 mg/ml solution of Versed.[173] Similarly, Dr. Robert M. Julien, formerly Associate Professor, Departments of Anesthesiology and Pharmacology, Oregon Health Sciences University, wrote the company on February 18, 1987:

> A typical 60 kg., elderly, debilitated patient is brought to the endoscopy, radiology or bronchoscopy suite after a small dose of narcotic premedication (a common situation). The dosage of 0.035 mg/kg (2.1 mg. in this patient) is reduced by 60%[174] to give a total dose of 0.84 mg/kg. Administered as you suggest over a 3 minute period implies a dose of 0.28 mg/minute. This translates to a minute volume injected of 0.056 cc/minute. I would state to any jury that 56/1,000 of a single cc[175] is virtually impossible for any physician to accurately inject by any known human technology. In other words, the presentation of Versed is not only impractical, it is dangerous and any indication on your part that drug overdosage is the sole responsibility of the physician[176] is blatantly wrong. The dosage presentation [of 5 mg/ml] should be altered by a factor of five. A concentration of 1 mg/cc would greatly reduce the overdoses that currently occur.[177]

Dr. Julien appealed to Roche's sense of "corporate responsibility" in urging a dilution of the solution concentration for the drug.[178]

It was not until July 1987, more than two years after the concentration of the intravenous solution of Versed was reduced in the United Kingdom that a more dilute, 1 mg/ml. solution of the drug was first made available to U.S. physicians.[179] Thereafter, Roche strongly endorsed use of this concentration to minimize the likelihood of oversedation. For example, in its November 1987 "Dear Doctor" warning letter, the company stated: "Since some patients may respond to as little as 1 mg, we strongly recommend the use of the 1 mg/mL formulation to facilitate slow titration to the desired endpoint of conscious sedation." [180]

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[167] The February 1985 issue of *Current Problems* is discussed in the May 10 Hearing, galley page 26.

[168] Ibid.

[169] FDA has advised the subcommittee that "[w]e have no record of a United Kingdom regulatory publication being submitted to the Food and Drug Administration." Hearings, Appendix I. In fact, FDA did not learn of this publication until it received a copy of it in a July 28, 1986, letter from the United Kingdom's Department of Health and Social Security, months *after* the drug was approved and attention had been focused on Versed-associated respiratory depression in the United States. Ibid.

[170] See the testimony of FDA medical officer, Dr. David L. Scally, May 10 Hearing, galley page 27.

[171] May 10 Hearing, galley page 27. According to a Roche tape of an October 18, 1986, meeting of several anesthesiologists on Roche's advisory board for Versed, Dr. Paul White of Stanford Medical School, a board member and Versed clinical investigator, stated: "They [endoscopists] are given 5 mg. These guys can't dilute it. We [anesthesiologists] have a bag of fluid. We just reach up and draw it up on a syringe. And that's the problem. That's why *several years ago*, Reves [J. R. Reves, a Versed clinical investigator and professor of anesthesiology at Duke University Medical School] and half the other people here encouraged you [i.e., Roche] to come out with a more dilute solution. In Europe they have a more dilute solution. . . . [I]t's the wrong concentration. . . . It's not easy for them [i.e., endoscopists] to dilute it." Ibid.

[172] May 10 Hearing, galley page 26.

[173] See page 1-77 of the verbatim transcript of that meeting, which is in subcommittee files.

[174] The Versed package insert recommends such a reduction for patients who, in addition to being elderly and debilitated also receive narcotic premedication.

[175] Dr. Julien testified that this represents "much less than a drop. . . ." May 5 Hearing, galley page 13.

[176] In early 1987, more than one year after the drug was approved, Roche for the first time included the following statement in the Versed package insert: "For ease of titration, Versed may be diluted with 0.9 percent sodium chloride or 5 percent dextrose in water to two to five times the original volume." May 5 Hearing, galley page 21. Dr. Julien testified that this measure was

> . . . grossly inadequate, because it places the onus for drug use entirely on the physician, attempting to take it off the manufacturer. . . . In addition, many people in endoscopy or bronchoscopy or other nonanesthesiologists, don't have the fluids readily available to them to make these dilutions. In addition, you then have in your work area, two different syringes. You have the original company syringe plus you have one that you have had to dilute up, and that adds an additional problem of having two different concentrations available for what we call syringe swaps or making a mistake and grabbing the wrong syringe and injecting it.

May 5 Hearing, galley page 21.

[177] Hearings, Appendix I.

[178] Ibid.

[179] FDA approved Roche's application to market this more dilute solution on May 26, 1987 and it was launched in July 1987, according to a September 1, 1987, letter to FDA from Roche. May 10 Hearing, galley page 28.

[180] Hearings, Appendix I.

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3. Promulgating Regulations Requiring the Submission of Potentially Important Information Related to Foreign Use of a New Drug Under FDA Review.

On the basis of its review of FDA's regulation of the new drug Merital, the committee recommended last year that FDA require sponsors to submit information relating to the foreign marketing and investigation of new drugs under agency review, including, "all labeling approved by foreign regulatory agencies; all standardized warning or information letters distributed to practitioners, pharmacists, and other health professionals in foreign nations; and accounts of all important regulatory developments concerning such drugs in foreign countries." [181]

Dr. Carl Peck, Director, FDA's Center for Drug Evaluation and Research, advised the subcommittee that FDA is developing a "guideline" calling for drug sponsors to submit such information to the agency.[182] If FDA agrees that it should have the information called for by this guideline, the committee believes the agency should require its receipt by *regulation.*

Conceding during his appearance before the subcommittee that "[b]y definition, a guideline, as such, does not have the force of law," [183] FDA Chief Counsel Scarlett testified that violations of a guideline would carry penalties if they also constituted violations of the Food, Drug, and Cosmetic Act (Act).[184] Pursuant to the congressional mandate that drug sponsors establish and maintain records and make such reports as the Secretary of Health and Human Services finds necessary, the Act authorizes the Secretary to promulgate *"regulations,"* not guidelines, to enforce this mandate.[185] Mr. Scarlett acknowledged before the subcommittee that a violation of an interpretative guideline, unlike that of a regulation, does not constitute a per se legal violation. A guideline, he testified, "usually attempts to provide objective guidance in relation to complying with some other standard which usually does have the

[181] See *FDA's Regulation of the New Drug Merital*, supra, page 94.

[182] Dr. Peck testified that the guideline will call for

> . . . reports obtained from foreign regulatory authorities, including reports of, or analyses of, adverse effects, warning letters sent to physicians, and major changes in marketing status or labeling information resulting from marketing or other experience. A copy should be provided of any letter from a foreign regulatory body that refuses drug approval on safety grounds. . . . Important differences from proposed U.S. labeling with respect to contraindications, warnings, precautions, adverse reactions, or dosing instructions should be emphasized.

May 5 Hearing, galley page 49.

[183] May 10 Hearing, galley page 10.

[184] May 10 Hearing, galley page 11.

[185] Section 505(i)(3) of the Act states that the Secretary shall "promulgate *regulations*" providing for "the establishment and maintenance of such records, and the making of such reports to the Secretary, by the manufacturer or the sponsor of the investigation of such drug, of data (including but not limited to analytical reports by investigators) obtained as the result of such investigational use of such drug, as the Secretary finds will enable him to evaluate the safety and effectiveness of such drug in the event of the filing of" a new drug application (NDA). (Emphasis supplied). Section 505(j)(1) states that the NDA holder for an approved drug shall "establish and maintain such records, and make such reports to the Secretary, of data relating to clinical experience and other data or information, received or otherwise obtained by such applicant with respect to such drug, as the Secretary may by general *regulation*, or by order with respect to such application, prescribe on the basis of a finding that such records and reports are necessary in order to enable the Secretary to determine, or facilitate a determination, whether there is or may be ground for invoking subsection (e) of this section . . ." (Emphasis supplied)

force of law, presumably the reporting requirements in the regulations." [186] Thus, Mr. Scarlett acknowledged,

> . . . in order to demonstrate the violation of a regulation based on the violation of a guideline, the FDA might have to offer evidence relating the factual allegations to the regulatory standard, whereas if something is in the regulation, then the agency wouldn't have to offer evidence on that but simply point to the regulation. If you have violated a guideline, the agency may have to offer more evidence to demonstrate that you've also violated a regulation.[187]

The committee believes that the greater evidentiary burdens that would attend enforcement of a guideline would lessen the probability of industry compliance with it.

During his appearance before the subcommittee, Mr. Scarlett defended the agency's proposed guideline approach on the grounds that "you don't want to overburden the regulations themselves with a lot of detail." [188] The committee notes, however, that, when deemed necessary or appropriate, agency regulations, such as those applicable to tests and methods of assay of antibiotic and antibiotic-containing drugs,[189] have been exceedingly detailed. The committee believes that the issue should turn, not on the degree of regulatory detail involved, but rather on the importance of the information called for in furthering FDA's capacity to protect the public from unsafe, ineffective, or misbranded new drugs.

Mr. Scarlett also noted in his testimony that

> . . . it is simpler for the agency to put out guidelines than it is to go through the fairly complicated process of putting together a regulation and getting that through the system. I think you can often get results quicker by indicating to the industry exactly what you want in the form of a guideline.[190]

Because guidelines can be put into effect much more expeditiously than regulations, the committee recommends that FDA issue guidelines that will remain in effect pending the completion of notice and comment rulemaking.

E. ROCHE DID NOT MAKE TIMELY REPORTS TO FDA OF IMPORTANT INFORMATION PERTINENT TO THE SAFE USE OF VERSED

1. Roche's Failure To Report Versed-Associated Deaths

On May 30, 1986, the Drugs Commission of the German Medical Profession published a warning on Versed-associated apnea and cardiac arrest.[191] The subcommittee's investigation revealed that

[186] May 10 Hearing, galley page 10.

[187] May 10 Hearing, galley page 15.

[188] May 10 Hearing, galley page 10.

[189] See 21 CFR 436.

[190] May 10 Hearing, galley page 10.

[191] See the May 30, 1986, *Deutsches Artzeblatt* article entitled, "Take Care When Giving Midazolam!", May 5 Hearing, galley page 67. FDA was first informed about this publication in an August 19, 1987, Roche submission.

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this warning was largely based on fatal cases involving use of the drug for conscious sedation that were known to Hoffmann-La Roche prior to FDA approval but were not reported to FDA until June 3, 1986,[192] more than five months *after* approval and only after publication of the warning in Germany.[193] On June 3, 1986, Roche reported to FDA eight serious cases of respiratory depression associated with foreign marketing of Versed,[194] five of which had proven fatal.[195] Although all five of these cases were known to Hoffmann-La Roche prior to FDA approval, only one of them had previously been reported to FDA before approval, and then had only been briefly summarized in a July 26, 1985, submission to the agency.[196]

When Hoffmann-La Roche reported these fatalities on June 3, 1986, it acknowledged that they were both "serious" and "unlabeled" (i.e., not listed in the approved labeling).[197] To be certain, these cases played an important role in FDA's post-market review of the drug's safety. Dr. Gerald Faich, Director, FDA's Office of Epidemiology and Biostatistics, testified that they were partly responsible for prompting FDA "to actively make inquiries of foreign authorities about the occurrences of other cases." [198]

Records obtained from Hoffmann-La Roche indicate that a *total of at least six deaths* involving respiratory depression associated with foreign marketing of Versed were known to Hoffmann-La Roche by approval time, but were not reported to FDA until after approval.[199] Five of these deaths involved endoscopies. In addition, several nonfatal but serious cardiorespiratory reactions to Versed reported to the company before approval were not forwarded to FDA until after approval.[200]

FDA testified before the subcommittee that Hoffmann-La Roche *was required* to report these cases *before* the drug was approved in December 1985. Section 314.50(d)(5)(vi)(b) of FDA's regulations re-

[192] May 5 Hearing, galley page 68.

[193] In an August 19, 1987, letter to FDA, Roche indicated that this warning was based on several "reports of apnea or cardiac arrest," including three German deaths, that were reported to FDA "on June 3, 1986," four days *after* the warning was published in West Germany. May 5 Hearing, galley page 68.

[194] Ibid.

[195] May 5 Hearing, galley page 68.

[196] Ibid. On July 26, 1985, Roche submitted an international safety update to FDA that included line summaries on two fatal and 10 nonfatal cases involving respiratory depression, as well as a prose summary of another fatal case. In a December 10, 1985, review of this update, Dr. David Scally discussed the fatal case described in the prose summary, which involved the death of a 61-year-old man that he did not attribute to the drug. Hearings, Appendix I. His review took no note of the two other deaths briefly reported on July 26, 1985, or of any of the other nonfatal respiratory depression cases reported on that date. Roche more fully reported one of these two deaths, which involved a 76-year-old man who underwent a gastroscopy, to FDA on September 11, 1987. In a similar vein, there does not appear to be any record establishing that an FDA medical officer had reviewed Roche's June 12, 1984, report to the Versed IND of the death of a 72-year-old man from cardiac arrest and respiratory failure given 0.21 mg/kg of Versed for a gastroscopy. This case was included among three cases of respiratory depression discussed in a May 17, 1984, letter from the United Kingdom's Committee on Safety of Medicines to Roche's U.K. affiliate. The June 12, 1984, report to the Versed IND is in subcommittee files.

[197] May 5 Hearing, galley page 68. In her June 3, 1986, submission to FDA, Dr. Loretta M. Itri, Director of Roche's Clinical Safety Surveillance Department, so characterized the cases. The company reiterated this conclusion in a June 25, 1986, letter to FDA. Ibid.

[198] May 5 Hearing, galley page 71.

[199] May 5 Hearing, galley page 71. Subcommittee staff review revealed that Hoffmann-La Roche also failed, prior to FDA approval, to report to the agency several cases of Versed-associated deaths not involving respiratory depression that had been brougbt to its attention

[200] May 5 Hearing, galley page 72.

quire an NDA sponsor, following receipt of an approvable letter, to update the NDA with "new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling." [201] Dr. Paula Botstein, Deputy Director, Office of Drug Evaluation I, testified that, pursuant to this regulation, Hoffman-La Roche was required to include any previously unreported Versed-associated respiratory arrest deaths known to it in a safety update submitted to the Versed NDA between its receipt of FDA's November 8, 1985, approvable letter for Versed and agency approval of the drug on December 20, 1985.[202]

The committee also believes that pre-market reports of these cases to FDA were required under FDA's IND regulations. Prior to FDA approval, Roche was required by Section 312.1(a)(6) of these regulations "promptly" to report to FDA "any finding" associated with a new drug under investigation "that may suggest significant hazards, contraindications, side effects, and precautions pertinent to the safety of the drug." [203] The committee believes that deaths that played an important role in FDA's decision to contact foreign nations for any additional information on similar cases certainly qualify as "significant" events within the meaning of this subsection.

In acknowledging to FDA on June 3, 1986, that several previously unreported cardiorespiratory reactions to Versed—including many of these deaths—were both "serious" and "unexpected" within the meaning of Section 314.80 of FDA's postmarket reporting regulations, Roche conceded that they were required to be reported to FDA within 15 working days following the drug's approval.[204] Inasmuch as none of these deaths were reported within this timeframe, the committee finds that Roche, by its own admission, failed to comply with the agency's legal reporting requirements.

During his appearance before the subcommittee, however, Dr. Gerald Faich, Director, FDA's Office of Epidemiology and Biostatistics, testified that

> . . . reports that had an origin in 1984 were actually not covered by the NDA rewrite that talked about 15 day submission of serious unlabeled reactions. That is, those regulations were not intended, I don't believe, to be retrospec-

[201] May 5 Hearing, galley page 73.

[202] May 5 Hearing, galley page 73.

[203] May 5 Hearing, galley page 70. On March 19, 1987, FDA issued rewritten IND regulations which replaced this subsection. Newly drafted Section 312.32 of FDA's IND regulations requires sponsors to notify the agency within *10 working days* of all "serious" and "unexpected" adverse reactions associated with a new drug under clinical investigation. See 52 Fed. Reg. 8797, 8837. A "serious" reaction "means any experience that suggests a significant hazard, contraindication, side effect, or precaution" and "includes any experience that is fatal." An "unexpected" reaction is one "that is not identified in nature, severity, or frequency in the current investigator brochure; or, if an investigator brochure is not required, that is not identified in nature, severity, or frequency in the risk information described in the general investigational plan or elsewhere in the current application, as amended." That Roche on June 3, 1986, categorized several of these deaths as both "serious" and "unlabeled" within the meaning of Section 314.80 of FDA's *postmarket* reporting regulations provides strong evidence that they also would have been "serious" and "unexpected" within the meaning of Section 312.32 of FDA's IND regulations.

[204] Section 314.80(c)(1) of FDA's regulations requires that serious and unexpected (i.e., "not listed in the current labeling for the drug") adverse reactions associated with the use of approved new drugs be reported to FDA "within 15 working days of initial receipt of the information."

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> tively applied. . . . I am telling you that the reporting and submission of foreign post-marketing reports of deaths such as apnea was [sic] clarified in August 1985. Prior to that, it was not in the post-marketing regulations. It wasn't 314.80 that applied to the submission of those reports.[205]

That the 15-day postmarket reporting requirements of Section 314.80 of the NDA rewrite did not go into effect until August 1985 is irrelevant to Roche's post-approval reporting obligations in this instance *since Versed was approved several months after this, in December 1985.*[206]

2. Roche's Failure To Report Important Clinical Trial Data

As earlier discussed, a study published in May 1988 by White et al. in *The Journal of Plastic and Reconstructive Surgery* suggested that the Versed conscious sedation doses originally approved by FDA were excessive. The subcommittee's investigation revealed that the results of this study were available to Roche prior to FDA approval, but not reported to the agency until several months after approval.

The White study was actually conducted under Roche's IND for Versed, the protocol for which was submitted to that IND on April 13, 1982.[207] The clinical portion of the study was completed in the first half of 1984.[208] A draft statistical report of the study findings was completed by November 28, 1984, more than one year *before* FDA approved Versed on December 20, 1985.[209] On February 5, 1985, more than 10 months before FDA approval, this report was designated as "final."[210]

[205] May 5 Hearing, galley page 69.

[206] Furthermore, any implication that fatal Versed-associated cardiorespiratory reactions occurring outside the United States would not have been subject to 15-day reporting requirements had Versed been approved prior to August 1985 is incorrect. Section 310.300(b)(2)(i) of FDA's regulations, which was superseded by Section 314.80 that month, set forth as subject to 15-day reporting requirements information related to an approved drug

> . . . concerning any unexpected side effect, injury, toxicity, or sensitivity reaction or any unexpected incidence or severity thereof associated with clinical uses, studies, investigations, or tests, whether or not determined to be attributable to the drug . . . 'Unexpected' as used in this subdivision refers to conditions or developments not previously submitted as part of the new drug application or not encountered during clinical trials of the drug, or conditions or developments occurring at a rate higher than shown by information previously submitted as part of the new drug application, or than encountered during such clinical trials.

The Justice Department cited this regulation in prosecuting SmithKline Beckman Corporation for failing to report to FDA serious liver toxicity associated with foreign use of its antihypertensive drug, Selacryn (ticrynafen), and Eli Lilly and Company for failing to report fatal hepato-renal reactions outside the United States to its anti-arthritis drug, Oraflex (benoxaprofen). See Elements of the Offense and Factual Basis for the Pleas, in *United States* v. *SmithKline Beckman Corporation*, United States District Court for the Eastern District of Pennsylvania, Criminal No. 84-00227, in subcommittee files; and *United States* v. *Eli Lilly and Company and William Ian H. Shedden*, United States District Court for the Southern District of Indiana, Criminal Nos. IP85 53 CR and IP85 54 CR, in subcommittee files. Insofar as cardiorespiratory fatalities associated with foreign use of Versed reveal an "unexpected' side effect of the drug, or a reaction to Versed of "unexpected . . . incidence or severity" within the meaning of Section 310.300(b)(2)(i), the committee finds that Roche would have been required to report them to FDA within 15 working days, even had Versed been approved before the August 1985 effective date for Section 314.80 of the NDA rewrite.

[207] May 10 Hearing, galley page 18.

[208] This was revealed by a subcommittee staff review of case report forms for the study. May 10 Hearing, galley page 18.

[209] May 10 Hearing, galley page 18.

[210] Hearings, Appendix I.

FDA first learned at the subcommittee's May 10, 1988, hearing that the paper published by White et al. in May 1988 was *based on the data analyzed in this Roche report of 3½ years earlier.*[211] As earlier discussed, Versed was originally recommended for use in conscious sedation at 0.1 to 0.2 mg/kg for healthy non-elderly adults. The November 1984 statistical report showed that *40 percent* of patients receiving *0.10 mg/kg* of Versed for *conscious* sedation became oversedated—that is, were put to sleep—and half of that 40 percent were unarousable. At *0.15 mg/kg, 75 percent* of patients became oversedated. *Four-fifths (⅘)* of these oversedated patients, or a staggering *60 percent* of all patients receiving *0.15 mg/kg* of the drug, were put to sleep and were unarousable. The report further indicated that significantly fewer Valium patients receiving twice these Versed doses became oversedated.[212]

Roche did not supply this report to FDA prior to the drug's U.S. approval. In fact, FDA advised the subcommittee that "the statistical report for the White study was submitted to the Food and Drug Administration on May 4, 1988," [213] one day before the subcommittee opened its hearings on the agency's regulation of Versed and then only after the subcommittee had requested and already received that report.

All of the important findings of the *statistical* report reappeared in Roche's *final* clinical report of this study, which was dated *September 4, 1985,* more than three months prior to FDA approval.[214] Despite this, the study was not included in the Summary Basis of Approval for Versed.[215]

In fact, this final report was not submitted to FDA until *September 26, 1986, nine months after approval,* in an annual report to the Versed IND.[216] Buried as it was in a voluminous, post-approval IND submission, this report, not surprisingly, apparently went unreviewed by FDA.[217] In fact, Dr. David L. Scally, FDA's medical reviewer for Versed, did not even become aware of the existence of this study report until shortly before the subcommittee's hearing, and only then because the subcommittee staff had been asking for "information on it." [218]

Dr. J.G. Reves, a Versed clinical investigator and Roche advisor on the drug, has concluded that the "most significant finding" in Dr. White's study is that Versed

> . . . has a steeper dose-response curve than [Valium]. This means that there may be less room for dosing error with [Versed]; in other words, overdose with [Versed] is easier to achieve than with [Valium]. [Versed's] steeper dose-re-

[211] May 10 Hearing, galley page 20. Dr. David L. Scally, FDA's medical reviewer for Versed, testified that he was not aware of this fact, while Dr. Carl Peck, Director, FDA's Center for Drug Evaluation, indicated that he was not even aware of the published paper: "I haven't had a chance to review the paper you're referring to. Published this month, you say?" Ibid.

[212] May 10 Hearing, galley page 20.

[213] Ibid. However, in an August 31, 1988, submission to FDA, which is in subcommittee files, Roche stated that this report was supplied to the agency on May 2, 1988.

[214] Ibid.

[215] May 10 Hearing, galley page 21.

[216] Ibid.

[217] See the testimony of Dr. David L. Scally, FDA's medical reviewer for Versed, Ibid.

[218] Ibid.

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> sponse curve suggests that vigilance is required when the drug is used for conscious sedation.[219]

To be certain, based on an assessment of sedation levels, the study revealed that the dose-response curve for Versed was markedly steeper than for Valium.[220] With Valium, as Dr. Robert M. Julien, formerly Associate Professor, Departments of Anesthesiology and Pharmacology, Oregon Health Sciences University, testified,

> . . . as you increase a dose over a fairly large range, you only get slight increases in sedation. You can increase a dose of Valium perhaps fivefold or sixfold in a patient and still not put them at great risk.[221]

By contrast, "very modest increases in dose" of Versed, he testified,

> . . . will take a patient from very light sedation to a patient who basically is in a state of general anesthesia. You have induced anesthesia, they are apneic, they are unresponsive. So the drug, while it is more potent, it is also less safe in that increases in dose produce a huge increase in response.[222]

Dr. Alan Lisbon, Assistant Professor of Anesthesia, Harvard Medical School, concurred with this assessment:

> There is no margin of safety with the drug because it has such a steep dose response curve. . . . With a drug like midazolam, . . . a little bit too much, because it is so potent, will have somebody stop breathing or run into cardiovascular and respiratory complications.[223]

Having established a "narrower therapeutic dosage range for midazolam," the White study concludes that "careful titration of midazolam using incremental doses of 1 to 2 mg to achieve the desired clinical effect is critically important to avoid overdosing patients" and producing "potentially life-threatening complications (e.g. apnea)." [224]

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[219] May 10 Hearing, galley page 19 and the reprint of his discussion of the paper by White et al. in Hearings, Appendix I.

[220] See, for example, the abstract of this study, Hearings, Appendix I. Dr. Carl Peck, Director, FDA's Center for Drug Evaluation and Research, acknowledged in his appearance before the subcommittee that the study shows that degree of sedation significantly increases with additional levels of the drug. May 10 Hearing, galley page 20.

[221] May 5 Hearing, galley page 26.

[222] May 5 Hearing, galley page 26.

[223] May 5 Hearing, galley page 20.

[224] May 5 Hearing, galley page 27 and the reprint of the study in Hearings, Appendix I. No respiratory depression was observed in this study, despite the considerable oversedation it documented, because, as Dr. Alan Lisbon, Assistant Professor of Anesthesia, Harvard Medical School, testified, patients were also given

> . . . another anesthetic drug, ketamine, which will help maintain respiration or breathing. Most people would not use the drug that way. By using ketamine they were able to blunt or take away the respiratory depression that one might see with midazolam.

May 5 Hearing, galley page 27. Thus, he took little consolation from the fact that respiratory depression did not accompany oversedation in this study, particularly since ketamine is not recommended for use in combination with Versed and would rarely be so used. May 10 Hearing, galley page 27.

The use of ketamine did not confound the reported comparison between Versed and Valium because the sedation levels recorded for each drug were assessed *after* patients initially received either of these drugs but *before* they received ketamine. May 10 Hearing, galley page 19. The published paper by White et al. states that the "degree of sedation was rated . . . 2 to 3 minutes

Continued

The White study also provides additional evidence of the significantly greater potency of Versed relative to Valium. That Versed patients, at one-half the dose given to Valium patients, experienced significantly more oversedation than their Valium counterparts, Dr. Robert M. Julien, formerly Associate Professor, Departments of Anesthesiology and Pharmacology, Oregon Health Sciences University, testified, "most certainly" suggested that Versed's "potency is more than twice that of Valium." [225] In fact, an abstract of the study stated: "With respect to its sedative properties, [Versed] was 2-4 times more potent than [Valium]," [226] a finding which, as Roche advisor and Versed clinical investigator, Dr. J.G. Reves, noted, "has obvious dosing significance." [227]

3. Roche's Failure To Report and Warn About the Markedly Greater Potency of Versed Relative to Valium

At the May 10, 1988, hearing, the subcommittee informed FDA that by June 1986, shortly after marketing of Versed began, Roche officials had privately concluded that the drug was *3 to 4 times as potent as Valium.*[228] On June 6, 1986, a preliminary draft of an article on Versed by *The Medical Letter on Drugs and Therapeutics,* which was circulated to Roche personnel for their review, stated that the drug was "about *twice* as potent . . . as" Valium.[229] (Emphasis supplied.) A Roche medical official subsequently recommended that this be changed to "3 to 4" times as potent. In accordance with this recommendation, Roche, in a July 3, 1986, letter to *The Medical Letter,* suggested that the publication

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after the initial dose of" Versed or Valium and, after that, "during the ketamine infusion." Accordingly, table IV of the paper reports sedation levels for "[a]fter initial sedative administration" of either Versed or Valium separately from those levels reported for "[a]fter ketamine administration." May 10 Hearing, galley page 19. Dr. J. G. Reves, a Versed clinical investigator and long-time Roche advisor on the drug, has written that the "paper by White . . . is a well-designed study that compares [Versed] and [Valium]" whose "most significant finding" is that Versed "has a steeper dose-response curve than [Valium]." Ibid. Obviously, Dr. Reves would not have made this observation were there any possibility that the initial sedation assessments reflected interactions between these drugs and ketamine.

[225] May 5 Hearing, galley page 26. Dr. White's paper was submitted for publication on February 27, 1987. See White, Vasconez, Mathes, Way, and Wender, supra, Hearings, Appendix I. At a March 14, 1987, Roche-supported symposium in Orlando, Dr. White summarized his findings as follows:

> One problem in comparing the potencies of midazolam and diazepam may relate to the fact that the slopes of the dose-response curves may not be parallel (figure) . . . Midazolam appears to have a steeper dose-response curve than diazepam, making it difficult to determine the exact potency ratio. Most investigators have reported that midazolam is twice as potent as diazepam. However, midazolam's more rapid onset of action as compared with that of diazepam makes midazolam appear to be even more potent . . . [W]e found during the operation itself, the supplemental dose of midazolam required was less than half that of diazepam, reflecting an even greater potency ratio between midazolam and diazepam.

See discussions section of "Midazolam in Plastic Surgery," in *Midazolam in Clinical Pharmacology,* ed. by Epstein and Reves, pages 15-16, in Hearings, Appendix I.

[226] Hearings, Appendix I.

[227] Hearings, Appendix I. Dr. Reves regarded the study as showing Versed to be "at least two to three times as potent as diazepam." See his commentary on the published paper by White et al., Hearings, Appendix I.

[228] May 10 Hearing, galley page 22. On April 23, 1986, approximately one month after U.S. marketing of Versed began, Roche received the first report of an American death associated with domestic marketing of the drug from a physician who advised a company official that, upon observing Versed's "activity," he thought Versed was *3 to 4 times as potent as Valium* and had, therefore, *reduced the Versed doses he gave to ¼ to ⅓ of those he gave of Valium.* A Roche memorandum written of a May 19, 1986, telephone conversation with the physician indicates that he conveyed this information to the company. May 10 Hearing, galley page 22.

[229] May 10 Hearing, galley page 22.

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characterize Versed as "*three to four times*" (Emphasis supplied.) rather than "twice" as potent as Valium.[230] This characterization did appear in the August 1, 1986, *Medical Letter* on Versed, but without any attribution to Roche.[231]

As FDA medical officer, Dr. David L. Scally testified, Roche did not reduce the recommended dose of Versed at this early stage of the drug's marketing to conform to this assessment of the drug's potency relative to Valium; [232] that is, doses were not reduced to ¼ to ⅓ of those recommended for Valium.[233]

Dr. Scally testified that he did not recall Roche's specifically advising him that it regarded Versed as three to four times as potent as Valium,[234] and, in a submission to the subcommittee hearing record, FDA has advised that

> . . . [w]e have been unable to determine from our review of our files when the Food and Drug Administration was informed that Versed was three to four times more potent than Valium. We are continuing to try to make that determination.[235]

In any event, the first "Dear Doctor" letter regarding cardiac and respiratory arrest during endoscopy that Roche sent to 100,000 physicians in February 1987 failed to warn that Versed was 3 to 4 times as potent as Valium.[236]

Eventually, however, Roche highlighted the importance of the markedly greater potency of Versed. On October 23, 1987, Roche advised FDA that future "[p]romotional campaigns will emphasize the potency of Versed relative to diazepam."[237] Accordingly, the

[230] May 10 Hearing, galley pages 22-3. At an October 18, 1986, meeting with Roche representatives, several of the company's consulting anesthesiologists similarly advised that they considered Versed to be 3 to 4 times as potent as Valium. See the transcription of selected excerpts from the tape recording of that meeting, Hearings, Appendix I.

Assessments of relative potency, to a great extent, are a matter of clinical impression, since as FDA medical reviewer, Dr. David Scally, wrote in a June 23, 1988, memorandum:

> I have evaluated no adequate and well controlled studies leading to a scientific conclusion that midazolam is much more potent than diazepam. For example, I cannot confirm anecdotal references to midazolam/diazepam ratios of 1/3, 1/3.5, 1/4, 1/5, etc. Nevertheless, it would now appear safer to presume a potency radio somewhere in this range when administering the initial and followup doses of intravenous midazolam.

In subcommittee files. It is particularly difficult to characterize the potency of Versed relative to Valium with scientific precision, since, as the paper published by White et al., supra, demonstrates, the dose-reponse curves for the two drugs may not be parallel.

[231] May 10 Hearing, galley page 23.

[232] May 10 Hearing, galley page 23.

[233] For safe measure, one consulting anesthesiologist informed Roche representatives at an October 18, 1986, meeting, that he advises physicians to administer Versed at *one-fifth* the dose they use of Valium. See the transcript of that meeting, Hearings, Appendix I.

[234] May 10 Hearing, galley page 22.

[235] Prior to the subcommittee's hearings, FDA staff had written that "[u]sing slurred speech as the endpoint, [Versed] was determined to be approximately 1.3 to 1.7 times as potent as [Valium]." May 5 Hearing, galley page 28. However, Dr. Robert M. Julien, formerly Associate Professor, Departments of Anesthesiology and Pharmacology, Oregon Health Sciences University, testified that, in his judgment, use of such an endpoint would have led to understating Versed's potency relative to Valium:

> Because at the point of slurred speech, you can still see respiratory depression and decreases in blood oxygenation. In addition, the drug has a slower onset of action than you would expect. If you titrate patients to the point of slurred speech, they will continue to absorb additional drug into the brain for several minutes after that point, so they actually become more deeply sedated following the point where you intended to go.

May 5 Hearing, galley page 29. As earlier discussed, the selection of slurred speech as a clinical endpoint may have been inappropriate.

[236] May 10 Hearing, galley pages 23-4.

[237] Roche's October 23, 1987, submission is in subcommittee files.

following month, approximately 17 months after Roche concluded Versed to be approximately three to four times as potent as Valium, the company highlighted this conclusion as the second sentence of a "Dear Doctor" warning letter [238] and, for the first time emphasized it in the bold-faced introduction to the Dosage and Administration section of the Versed labeling.[239]

F. FDA'S ENFORCEMENT OF ITS REPORTING REQUIREMENTS CONTINUES TO BE GROSSLY DEFICIENT

In the past, the committee, after documenting serious deficiencies in FDA's enforcement of its legal reporting requirements, has recommended that the agency substantially increase its commitment to ensuring industry compliance with those requirements. On the basis of its review of the Versed experience, the committee must conclude that FDA's performance in this critical law enforcement area remains woefully inadequate.

Most notably, FDA failed to investigate Hoffmann La-Roche's adverse reaction reporting practices for Versed, even though data FDA received from the company strongly suggested that the firm may have failed to submit to the agency reports of deaths known to it prior to the drug's U.S. approval.

When Roche reported several serious and sometimes fatal cases of respiratory and cardiac arrest to FDA on June 3, 1986, a few months after American marketing began, it forthrightly acknowledged that they "cover[ed] a two to three year period." [240] To be certain, all of these foreign cases were designated by "84" and "85" case numbers, [241] thereby indicating that they were logged into a Hoffmann-La Roche affiliate in 1984 or 1985. That these cases were reported to a company affiliate in 1984 or 1985 suggested that it was likely that most, if not all of them, were known to Hoffmann-La Roche prior to FDA approval in late December 1985. When confronted with these case numbers at the subcommittee's May 5, 1988, hearing, in fact, Dr. Paula Botstein, Deputy Director, Office of Drug Evaluation I, acknowledged that "[i]t may be the case" that the firm failed promptly to report to FDA a number of foreign deaths, including some that were known to it a year or more earlier.[242]

The committee notes that the subcommittee staff, on the basis of the company case numbers accompanying *postmarket* reports to FDA of Versed-associated deaths and other serious reactions, recognized possible reporting lapses the very first time it examined those reports. This prompted the subcommittee to request additional detailed information from Roche, [243] which confirmed receipt by

[238] May 10 Hearing, galley page 24. That letter opens: "Versed is a potent sedative agent which has been widely used for conscious sedation. Clinical experience indicates that it may be *three to four times as potent* per mg as diazepam (Valium)." (Emphasis supplied.) See that letter in Hearings, Appendix I.

[239] May 10 Hearing, galley page 24. Final printed labeling containing this conclusion was dated November 23, 1987. Roche submitted draft labeling with this conclusion to FDA on September 18, 1987.

[240] May 5 Hearing, galley page 69.

[241] May 5 Hearing, galley page 68.

[242] May 5 Hearing, galley page 73.

[243] See the subcommittee's October 9, 1987, letter to Mr. Irwin Lerner, President and Chief Executive Officer, Hoffmann-La Roche Inc., which is in subcommittee files.

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the sponsor and/or its foreign affiliates of several reports of serious and sometimes fatal Versed-associated adverse reactions prior to the drug's U.S. approval.

FDA's medical reviewer for Versed, Dr. David Scally, testified that he was not aware of these 1984–85 accession numbers,[244] even though in his September 10, 1986, and November 19, 1986, reviews of postmarket reports of serious cardiorespiratory reactions to Versed,[245] he used those company numbers to identify each reviewed case.

Dr. Scally testified that, initially, the "adverse experience results were not routed directly to me," but rather to FDA's Division of Neuropharmacological Drug Products (DNDP) and the agency's Office of Epidemiology and Biostatistics (OEB).[246] The record does not reveal a single instance in which any DNDP or OEB[247] reviewer who received and examined Roche's postmarket adverse reaction reports noticed that they had been logged into Hoffmann-La Roche's international system in 1984 and 1985, long before they were reported to FDA.

It is not surprising, therefore, that, in 1986, FDA did not investigate the circumstances surrounding the delayed reporting of the several cases reported to it in mid-1986. In fact, no agency inquiry was even contemplated until 1988, and then only as a result of a petition received from the Public Citizen Health Research Group[248] and after Roche had made available to FDA international adverse reaction data requested by the subcommittee,[249] which had already initiated such an inquiry after reviewing evidence of delayed reporting in some of the company's postmarket submissions to the agency.

As previous subcommittee investigations demonstrate, this is not the first time that FDA has not acted on evidence furnished to it suggesting that sponsors have not met their adverse reaction reporting obligations. For example, last year the committee found that the "conclusion that Hoechst did not comply with a wide array of agency adverse reaction reporting requirements" concerning its antidepressant, Merital (nomifensine maleate), was

> . . . largely based on information contained in FDA's files. [S]everal Hoechst submissions, on their face, show that the sponsor had not met its adverse reaction reporting requirements. . . .[250]

The committee expressed concern that "such noncompliance was not recognized by FDA prior to the subcommittee's May 22, 1986, hearing" on FDA's regulation of Merital.

In 1983 and again last year, we recommended that FDA "ensure that its personnel correctly interpret and strictly enforce all legal adverse reaction reporting requirements."[251] If FDA persists in its failure to require prompt reporting of serious adverse drug reactions, the committee concludes that it cannot ensure the American public protection from potentially unsafe and misbranded new drugs.

The committee is also concerned that some FDA personnel are insufficiently knowledgeable about the legal obligations of sponsors to report serious adverse reactions to the agency. For example, Dr. Paula Botstein, Deputy Director, Office of Drug Evaluation I, testified that adverse safety information derived from *foreign marketing* experience with a new drug was not required to be reported to the IND.[252] This testimony is belied by the historical record. As Chief Counsel Scarlett acknowledged, in considering the reporting practices of Eli Lilly and Company for the new drug, Oraflex (benoxaprofen), FDA determined that the IND reporting regulations "could be interpreted to require the reporting of foreign marketing experience."[253] Effective law enforcement demands that the agency ensure that all of its reviewing personnel are familiar with, and fully understand, the specific reporting obligations of new drug sponsors.

The committee also concludes that FDA has committed insufficient law enforcement resources to investigating suspected noncompliance with agency reporting requirements. For example, FDA initiated a major investigation of Hoechst's reporting practices for its antidepressant, Merital (nomifensine maleate), after the subcommittee supplied evidence to the agency in mid-1986 of Hoechst's failure to report to FDA a large number of deaths and other important adverse safety data associated with use of Merital prior to that drug's U.S. approval.[254] At the subcommittee's hearings concerning Versed *two years later*, FDA Chief Counsel Scarlett testified that the results of that "extensive investigation" had not yet arrived at his office.[255] Yet, on January 11, 1988, FDA's Office of Compliance recommended a grand jury investigation into Hoechst's adverse reaction reporting practices for Merital.[256]

In a similar vein, no action has been taken by FDA since it completed inspections in 1987 of the reporting practices of several Johnson & Johnson (J&J) subsidiaries—including McNeil Pharmaceutical and Ortho Pharmaceutical Corporation—in connection

[244] May 5 Hearing, galley page 68.
[245] Both reviews are in subcommittee files.
[246] May 5 Hearing, galley page 68.
[247] Notwithstanding the initial testimony of Dr. Gerald Faich, Director, Office of Epidemiology and Biostatistics, that post-market reports from 1984 and 1985 were not routed to his office, reports of this kind that were contained in Roche's June 3, 1986, submission to FDA were initially addressed to Dr. Julie Millstein of Dr. Faich's office. May 5 Hearing, galley page 68. When confronted with this evidence, Dr. Faich acknowledged that they "came to my office . . ." May 5 Hearing, galley page 69. When asked whether he was "aware that the case numbers were for 1984 and 1985," Dr. Faich testified that "I can't say that I was, but I think we agreed that those should be submitted at that point." Ibid.
[248] FDA has advised the subcommittee: "An internal review of the files was begun in February, subsequent to the receipt of a petition filed by Public Citizen on February 12, 1988." May 5 Hearing, galley page 74. In its February 12, 1988, petition to FDA, the Public Citizen Health Research Group requested that FDA "[d]etermine whether Roche fully and promptly informed FDA prior to U.S. approval of all British deaths from midazolam, British studies on midazolam, and the lower midazolam doses approved in Britain." Hearings, Appendix I. FDA's "internal review" of Roche's reporting practices was in such as embryonic stage by the subcommittee's May 5, 1988, hearing, that no FDA onsite inspection had yet been ordered of the company's files.
[249] On December 15, 1987, February 12, 1988, and March 15, 1988, Roche submitted to FDA the records it made available to the subcommittee.

[250] See *FDA's Regulation of the New Drug Merital*, supra, pages 71–2.
[251] May 5 Hearing, galley page 73.
[252] May 5 Hearing, galley page 70.
[253] May 10 Hearing, galley page 71. FDA subsequently requested a grand jury investigation into Lilly's failure to report deaths associated with use of Oraflex during foreign marketing of the drug.
[254] See *FDA's Regulation of the New Drug Merital*, supra, pages 47–80.
[255] May 10 Hearing, galley page 34.
[256] In subcommittee files.

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with J&J's analgesic, Suprol (suprofen).[257] Prior to this time, the subcommittee had advised FDA of J&J's failure to report promptly to FDA significant safety data concerning Suprol, including several studies in which single doses (or repeat single doses) of the drug produced acute kidney injury, including flank pain, in healthy young male volunteers.[258] Suprol was eventually withdrawn from the market after being associated with more than 300 reports of acute kidney damage in the United States, primarily in healthy young men.[259]

In a May 27, 1988, "post-mortem" meeting following the subcommittee's hearings on Versed, Mr. Scarlett reportedly stated:

> Why don't prosecutions happen faster? Why does it take so long to prepare and file a criminal prosecution case. *A priority* case? [260]

Inasmuch as the Statute of Limitations is running on potentially significant violations of agency reporting requirements, the committee shares these concerns and urges FDA to commit itself more vigorously to investigating and, where appropriate, recommending criminal prosecution of sponsors that have seriously violated those requirements.

G. NONCOMPLIANCE WITH FEDERAL REPORTING REQUIREMENTS MAY HAVE REACHED EPIDEMIC PROPORTIONS

The subcommittee's hearings on Versed marked the third set of hearings in two years where the subcommittee presented to FDA evidence suggesting that a drug manufacturer seriously violated legal reporting requirements.[261]

With each case, the committee becomes increasingly concerned that serious reporting lapses by major pharmaceutical companies may have reached epidemic proportions within some segments of the industry. At the very least, FDA has not been receiving information vital to protecting human health and safety. If FDA is to continue to enjoy the confidence of the American public, the committee believes it is imperative that it do a far better job of ensuring that it has the information required to regulate new drugs.

H. PHYSICIANS WERE INSUFFICIENTLY WARNED ABOUT THE RISKS OF VERSED-ASSOCIATED RESPIRATORY TOXICITY

The committee finds that for almost two years following Versed's approval, neither FDA nor Roche ensured that physicians were adequately warned about Versed's cardiorespiratory toxicity.

FDA did not require the February 1987 "Dear Doctor" letter on Versed-associated respiratory depression to be issued as a "Drug Warning" letter, even though deaths and other serious reactions

[257] See the testimony of FDA Chief Counsel Scarlett, May 10 Hearing, galley page 34. Also see FDA's submission for the hearing record, Hearings, Appendix I.
[258] Hearing before a Subcommittee of the Committee on Government Operations, "FDA's Regulation of the New Drug Suprol," May 27, 1987.
[259] Ibid.
[260] Notes of this meeting are in subcommittee files.
[261] See Hearing before a Subcommittee of the Committee on Government Operations, "Oversight of the New Drug Review Process and FDA's Regulation of Merital," May 22, 1986; and Hearing before a Subcommittee of the Committee on Government Operations, "FDA's Regulation of the New Drug Suprol," supra.

had already been reported for Versed, particularly when used by endoscopists for conscious sedation.[262] Section 200.5(c) of FDA's regulations requires that information in a "Dear Doctor" letter concerning "a significant hazard to health" be sent as a "Drug Warning" letter in an envelope bearing the words "Important Drug Warning" in large *red* letters.[263] FDA permitted the February 1987 letter to be sent as a far less precautionary "prescribing information" letter; that is, the envelope only bore the words "Important Prescribing Information" in blue letters.[264]

The result, if the experience of Dr. Douglas Walta, a Portland, OR, gastroenterologist, is representative, is that much of the target audience of the February 1987 letter was not alerted to the problems that had been reported for Versed. Dr. Walta testified that the letter didn't "grab" his "attention" because

> . . .[i]t didn't have a warning on it at all. It was just another standard letter, pushing Versed, like thousands of other drugs are pushed upon us. There was no red warning flag, no indication that this is something that better get your attention.[265]

By contrast, Dr. Walta testified,

> . . . the big red warnings when they come out, get everybody's attention. They recognize that something has happened to this product that made the FDA either force the drug company or encourage the company to communicate to us that there's a problem. A red warning gets my attention.[266]

Dr. Carl Peck, Director, FDA's Center for Drug Evaluation and Research, testified that in the months following the drug's marketing

> . . . the situation . . . was considered to be a serious signal deserving of careful evaluation. Indeed, the Office of Epidemiology and Biostatistics got into gear and began to have frequent safety conferences to review the data as it came in.[267]

The committee concludes, however, that that seriousness was not adequately imparted to the medical profession.

The February 1987 Dear Doctor letter also downplayed the potential seriousness of Versed-associated respiratory depression. Although by February 1987 FDA had received at least *16* reports of *fatal* Versed-associated cardiorespiratory reactions, the "Dear Doctor" letter Roche sent that month neglected to mention that deaths had been associated with the drug's use.[268] Yet, that same month the company added to the Versed package insert the statement that "respiratory depression, apneas, respiratory arrest and/

[262] May 10 Hearing, galley page 31.
[263] Ibid.
[264] Ibid.
[265] May 5 Hearing, galley page 13.
[266] May 5 Hearing, galley page 14.
[267] May 10 Hearing, galley page 31.
[268] May 10 Hearing, galley page 28.

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or cardiac arrest, sometimes resulting in *death*" [269] (emphasis supplied) had been associated with use of Versed.

During the subcommittee's hearing, Dr. Janet Arrowsmith, Medical Epidemiologist, FDA's Office of Epidemiology and Biostatistics, defended the omission of any mention of deaths on the grounds

> . . . that we did not consider the events reported to us totally unexpected. . . [I]n this case, respiratory depression and CNS depression is part of the desired effect of the drug and it is dose-dependent.[270]

Dr. Arrowsmith's testimony, however, does not make the case that death was an expected outcome of Versed use. Her testimony only establishes that *respiratory depression* was "not . . . totally unexpected" under some circumstances with Versed:

> When the drug is given at a higher than recommended dose, especially in the face of, for instance, meperidine, which is a CNS depressant, Fentanyl and phenobarbital, which many of these patients were receiving at the time that they got the Versed, giving the full dose, and in patients who are elderly, giving the full dose of Versed, respiratory depression is not unexpected.[271]

That respiratory depression is known to be a dose-related consequence of benzodiazepine use, particularly when other CNS depressants are used, does not mean that large number of *fatal* cardiorespiratory reactions to Versed were to be "expected". In fact, Dr. Arrowsmith's superior, Dr. Gerald Faich, Director, FDA's Office of Epidemiology and Biostatistics, testified before the subcommittee that "[t]here is an instance where death as an event, might be deemed expected and might not necessarily be anticipated or reportable—that is not the case with this drug, however, where death is not an expected event or at least wasn't early on." [272]

Dr. Arrowsmith also maintained that deaths need not have been mentioned in the February 1987 "Dear Doctor" letter because

> . . . cardiac arrest and respiratory arrest, if unattended, are fatal events. That's what it means. The heart has stopped and breathing has stopped. . . . So that it's redundant in some ways to say cardiac arrest, respiratory arrest or death.[273]

Mentioning that several deaths had been associated with Versed use, however, would certainly have underscored and alerted physicians to the gravity of failing to administer Versed under proper conditions. In fact, FDA medical officer, Dr. David Scally, noted in an October 1, 1986, draft of a proposed Versed "Dear Doctor" letter, that the "high mortality" observed in connection with reports of Versed-associated respiratory and cardiac arrest "dictates

[269] May 10 Hearing, galley page 29.
[270] May 10 Hearing, galley page 29. Dr. Arrowsmith testified that "among the first 17 cases that we received, when we evaluated these as to the unexpectedness, given concomitant drugs, the age of the patient, the setting, the use, the dose of midazolam, we only actually felt that one of those was unexpected." May 10 Hearing, galley page 28.
[271] Ibid.
[272] May 5 Hearing, galley page 72.
[273] May 10 Hearing, galley page 30.

that a reminder [about the conditions of safe use of the drug] is indicated." [274]

It is noteworthy that Roche justified its November 1987 "Dear Doctor" warning by explicit reference to the deaths associated with Versed's use. That letter, unlike its February 1987 predecessor, stated: "Because serious adverse events, including respiratory depression, apnea, cardiac arrest and *death*, have been associated with its use, we wish to reemphasize the need for careful individualized dosing." [275] (Emphasis supplied.) The November 1987 letter also introduced the new boxed warning that had been added to the Versed package insert, which similarly stated:

> Intravenous VERSED has been associated with respiratory depression and respiratory arrest, especially when used for conscious sedation. In some cases, where this is not recognized promptly and treated effectively, *death* or hypoxic encephalopathy has resulted.[276] (Emphasis supplied.)

The administrative record reveals that FDA requested this boxed warning emphasis on Versed-associated *deaths* in an October 9, 1987, letter to Roche.[277] Eventually, when left to its own devices, FDA, notwithstanding some of the agency's testimony before the subcommittee, considered it important to emphasize that *"death"* was the outcome of some reported cases of "respiratory arrest".

That Versed-associated cardiorespiratory arrest had proven fatal in several instances also could suggest that it may be significantly more difficult to resuscitate patients experiencing cardiorespiratory reactions to Versed than alternative drugs. In this connection, Dr. Douglas C. Walta, the Gastroenterology Clinic and Providence Hospital, Portland, Oregon, testified that, in his experience, respiratory depression induced by Valium could be far easier to counteract than that produced by Versed.[278]

FDA also understated the potential gravity of Versed-associated respiratory depression in its communication with health professionals. The April 1987 FDA Drug Bulletin on Versed-associated respiratory and cardiac arrest, like Roche's February 1987 "Dear Doctor" letter, failed to mention that many such reactions involved *deaths*.[279] The bulletin simply stated that "FDA has received 17 domestic reports" of serious cardiorespiratory reactions to Versed.[280] By April 1987, however, FDA had received *more than 17* reports of *fatal* cardiorespiratory reactions to the drug.[281] Prior to April 1987, FDA had received at least *19* reports of Versed-associated cardiorespiratory deaths and *35* total reports of serious cardiorespiratory reactions to Versed.[282]

[274] In subcommittee files.
[275] Hearings, Appendix 1.
[276] Ibid.
[277] This letter is in subcommittee files. This letter requested that Roche use the same language that was drafted by Dr. David Scally, FDA's medical reviewer for Versed, in an October 7, 1987, review, which is in subcommittee files.
[278] May 5 Hearing, galley page 6.
[279] May 10 Hearing, galley page 33.
[280] Ibid.
[281] Ibid.
[282] Ibid.

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IV. Recommendations

The committee regrets that many of the deficiencies found in this report have been identified by the committee in earlier reports, but FDA has failed to take adequate remedial action. These and the other deficiencies enumerated in this report should be corrected immediately. The committee specifically recommends that the Secretary of Health and Human Services promptly take steps to ensure that:

1. FDA receives and reviews all potentially important publications in the medical literature regarding the safety and efficacy of new drugs before it approves them for marketing.
2. FDA thoroughly examines all documents and files that might contain information important to assessing the safety or efficacy of new drugs under agency review. The agency should consider the feasibility of consolidating the companion IND and NDA files for any new drug following the submission of a new drug application for that drug.
3. FDA promulgates regulations requiring sponsors to submit to it information from foreign nations relating to new drugs under agency review, including
   (a) all labeling approved by foreign regulatory authorities;
   (b) all standardized warning or information letters distributed to practitioners abroad;
   (c) all reports and analyses obtained from foreign regulatory authorities of adverse drug reactions and other significant aspects of the toxicity of such drugs;
   (d) all correspondence and related documents received from foreign regulatory agencies related to any denial of marketing approval on safety grounds; and
   (e) accounts of all important regulatory developments, including major changes in marketing status or labeling information, in connection with the use of such drugs outside the United States.

The committee recommends that FDA publish guidelines calling for the aforementioned information that will remain in effect pending completion of notice and comment rulemaking.

4. FDA vigorously enforces all legal adverse reaction reporting requirements applicable to new drug sponsors. FDA should alert its new drug reviewers, on a periodic basis, to the need for prompt investigation of all evidence received of potentially serious breaches of these requirements. Towards this end, FDA should take immediate steps to guarantee that its reviewers are familiar with and understand the specific reporting obligations of new drug sponsors.
5. FDA permit "Dear Doctor" letters designed to caution practitioners about potentially serious drug safety problems to be issued only as "Drug Warning" letters in accordance with the procedures set forth in Section 200.5(c) of FDA's regulations.

ADDITIONAL VIEWS OF HON. JIM LIGHTFOOT, HON. FRANK HORTON, HON. WILLIAM F. CLINGER, JR., HON. AL McCANDLESS, HON. LARRY E. CRAIG, HON. HOWARD C. NIELSON, HON. JOSEPH J. DioGUARDIA, HON. DONALD E. "BUZ" LUKENS, HON. AMORY HOUGHTON, JR., HON. J. DENNIS HASTERT, AND HON. JAMES M. INHOFE

The Committee plays an important oversight function. It is the Committee's responsibility to review and study the operation of government activities at all levels, including the regulation of drugs and other products by the Food and Drug Administration (FDA). In reviewing these activities, the Committee must strive to present as fair and complete of a picture as possible.

In the case of this report, the Committee has raised a number of legitimate concerns that question FDA's regulation of the new drug Versed. For example, the Committee finds that the drug sponsor did not submit timely reports to FDA of important information and that FDA was not familiar with foreign marketing of Versed. The Committee assumes that if FDA had been aware of this information, then many of the problems associated with the use of Versed could have possibly been avoided. This could be the case; however, it will be FDA's responsibility to determine whether knowledge of this information would have made a difference in the regulation of the drug.

In light of the Subcommittee's investigation and the Committee's report, as well as the Public Citizen Health Research Group's citizens' petition on Versed, we would expect that FDA will review closely the issues that have been raised. We note that at this time no definitive answers have been put forward. Therefore, we will await FDA's review of this matter before we make any indictments on whether information was submitted in a timely manner and whether FDA appropriately reviewed important information.

Another point we would like to address is the role of medical mismanagement in the safety and use of Versed. When FDA began to receive adverse drug reaction reports, there were some concerns that the drug was not being used properly and that adequate monitoring of the patient during use was not occurring. In light of these concerns, FDA and the drug sponsor initiated steps to inform the medical community of among other things the importance of individualizing the dosage, administering the drug slowly, and monitoring the patient closely. We believe these steps, i.e. "Dear Doctor letters and revised labeling, were beneficial in informing the medical profession of the precautions that were needed when using this drug.

The Committee, however, raises a question about whether the first "Dear Doctor" letter was suficient to warn physicians about problems with Versed. The Committee finds that a "Drug Warning" letter would have been more appropriate than a letter discuss-

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ing drug prescribing information. Witnesses at the hearing indicated that they often don't read all of their mail, such as "Dear Doctor" letters, because of the enormous amount of promotional and other material they receive. While we can sympathize with them on this issue, we also believe that more care needs to be taken physicians to review material which will assist them in performing their jobs.

In addition, we would encourage FDA to review whether "Dear Doctor" letters are effective in relaying information to physicians. If these letters are going unread because they do not have a "Drug Warning" message on the envelope, then perhaps FDA should devise an alternative system to inform physicians about important drug information.

The final issue which we would like to address is the objectivity of the hearing held on Versed. While we fully support the role of the Subcommittee to conduct oversight on FDA's activities and while we believe that the Committee has raised legitimate concerns in this report, we question whether the original hearing was held in as fair and as objective manner as possible. For example, minority members of the Subcommittee were not informed of the hearing until reading about it in a trade publication. They were also not informed of who would be testifying until less then 24 hours before the hearing, although the majority of the witnesses were invited to testify five to six weeks prior to the scheduled date of the hearing. In addition, it appeared that a balanced picture of Versed was not sought.

Versed is a potent drug, and is one that should be used with care. Inappropriate use of Versed can result in adverse reactions. However, the drug has been and continues to be used successfully by many anesthesiologists and gastroenterologists, which, in our opinion, was not a picture presented by the non-FDA witnesses at the hearing. Two of the witnesses testified about their experiences with Versed. In both cases, they had patients whose deaths were associated with the use of Versed. Naturally they testified that they would never use Versed again.

However, what was not told about the two fatalities was that when FDA reviewed the cases, other factors could have played an important role in the fatal reaction. For instance, FDA's assessment of one case was that "the Versed dose was excessive considering the patient age and concomitant narcotic exposure" and that "the contrast dye may have been the precipitating agent"; FDA's assessment of the other case showed among other things that "Versed was not being used for an approved indication and was not administered in an appropriate dose or by an approved and appropriate method." (May 12, 1988, Memo from Drs. Arrowsmith and Faich to the Hearing Record, Appendix 2)

We believe that a different perspective on Versed should be presented at this time. In a June 28, 1988, response to a letter from Congressman Lightfoot about his experiences with Versed, Dr. J.G. Reves, a Professor of Anesthesiology at the Duke University Medical Center, wrote:

> * * * I would state that Versed has been an important new addition to the formulary. In my own practice I use it every day in every patient that I care for. I have had absolutely no complications from this drug which is clearly superior to Diazepam and other benzodiazepines in my practice. In my own clinical practice and in a number of clinical investigations with this drug I have found it to be a very predictable and effective compound of great value to clinicians." (Hearing, Appendix 2)

In a June 1, 1988, letter to Congressman Lightfoot, Dr. Stanley B. Benjamin, Chief of the Division of Gastroenterology at Georgetown University Hospital, wrote:

> It is my sincere belief that we can not blame the drug for what would appear in many situations to be (a) lack of monitoring of patients under their care. I believe this drug is a(n) important part of the safe and effective practice of Gastroneterology but it must be used with caution and respect. (Hearing, Appendix 2)

Another comment received was from Dr. David Fleischer, Chief of the Endoscopy Unit at Georgetown University Hospital; he wrote in a July 5, 1988, letter that:

> I personally, and the majority of my colleagues, feel that midazolom (Versed) presents a significant advance over diazepam (Valium) for patients who undergo endoscopic procedures. It is shorter-acting and the amnesic effect is greater. I believe there is nothing intrinsically more dangerous about midazolom than diazepam and I believe that if appropriate monitoring precautions are taken, the drug can continue to be a useful and valuable product for the care of patients with gastrointestinal diseases who undergo endoscopic procedures. (Hearing Appendix 2)

Granted, others might have different views on Versed, but the central point is that a balanced picture be presented.

In conclusion, we believe the Committee has raised some significant questions which need further exploration. We also believe that our oversight responsibilities as it pertains to the FDA can significantly improve the safety of drugs used by the American public. We would hope that the Committee continues to exercise its responsibilities in this area in as objective and complete manner as possible.

JIM LIGHTFOOT.
FRANK HORTON.
WILLIAM F. CLINGER, JR.
AL MCCANDLESS.
LARRY E. CRAIG.
HOWARD C. NIELSON.
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Exhibit D

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Union Calendar No. 332

98th Congress, 1st Session - - - - - - - - - House Report No. 98-584

FDA'S REGULATION OF ZOMAX

THIRTY-FIRST REPORT

BY THE

COMMITTEE ON GOVERNMENT OPERATIONS

together with

ADDITIONAL AND DISSENTING VIEWS

DECEMBER 2, 1983.—Committed to the Committee of the Whole House on the State of the Union and ordered to be printed

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LETTER OF TRANSMITTAL

HOUSE OF REPRESENTATIVES,
Washington, D.C., December 2, 1983.

Hon. THOMAS P. O'NEILL, JR.,
Speaker of the House of Representatives,
Washington, D.C.

DEAR MR. SPEAKER: By direction of the Committee on Government Operations, I submit herewith the committee's thirty-first report to the 98th Congress. The committee's report is based on a study made by its Intergovernmental Relations and Human Resources Subcommittee.

JACK BROOKS, *Chairman.*

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Union Calendar No. 332

98TH CONGRESS } HOUSE OF REPRESENTATIVES { REPORT
1st Session } { No. 98-584

FDA'S REGULATION OF ZOMAX

DECEMBER 2, 1983.—Committed to the Committee of the Whole House on the State of the Union and ordered to be printed

Mr. BROOKS, from the Committee on Government Operations, submitted the following

THIRTY-FIRST REPORT

together with

ADDITIONAL AND DISSENTING VIEWS

BASED ON A STUDY BY THE INTERGOVERNMENTAL RELATIONS AND HUMAN RESOURCES SUBCOMMITTEE

On November 15, 1983, the Committee on Government Operations approved and adopted a report entitled "FDA's Regulation of Zomax." The chairman was directed to transmit a copy to the Speaker of the House.

I. INTRODUCTION

Under the Rules of the House of Representatives, the Committee on Government Operations has responsibility for studying the operation of Government activities at all levels from the standpoint of economy and efficiency. The committee has assigned this responsibility as it relates to the Department of Health and Human Services (HHS) to the Intergovernmental Relations and Human Resources Subcommittee.

Few governmental activities affect the public's health more than those involved in determining whether powerful new drug products are safe and effective for human use. For this reason, a high priority of the subcommittee has been to examine the administrative performance of the Food and Drug Administration (FDA) in protecting the public from unsafe and ineffective drugs.

FDA's regulation of the pain reliever, Zomax (generic name zomepirac sodium), had been the focus of an ongoing subcommittee investigation into FDA's policies and procedures for assuring the safety of new drugs when its manufacturer, McNeil Pharmaceutical, a subsidi-

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of Johnson and Johnson, withdrew Zomax from the market on
h 4, 1983, because of a large number of serious allergic reactions,
ding deaths, associated with its use.
ne subcommittee's investigation of FDA's regulation of Zomax in-
d two days of public hearings on April 26 and 27, 1983.[1] Wit-
s included the Commissioner of the Food and Drug Administra-
an expert toxicologist, practicing physicians and Zomax patients,
representatives of McNeil Pharmaceutical.
ne subcommittee also examined the relevant scientific literature
FDA documents, including correspondence, internal memoranda
reports, safety and efficacy reviews, verbatim transcripts of FDA
sory committee meetings, and information contained in new drug
lication (NDA) and investigational new drug (IND) files. The
prehensive nature of this review has enabled the subcommittee
valuate FDA's policies and procedures for approving and regu-
ng the use of Zomax, and, by extension, new drugs in general.

II. Background

DA approved Zomax on October 28, 1980, for the relief of mild
moderately severe pain. Zomax was the first nonsteroidal anti-
ammatory drug (NSAID) approved for this purpose.[2]
omax was synthesized in 1969 by its manufacturer, McNeil Phar-
eutical (McNeil).[3] McNeil submitted an investigational new drug
plication (IND) for Zomax on July 22, 1974, and a new drug
plication (NDA) on December 18, 1978. Approximately 3,600 users
ticipated in the Zomax clinical trials in the United States.
Zomax is the only approved nonsteroidal anti-inflammatory drug
sidered by FDA to pose a possible cancer risk to humans. Because
its carcinogenic potential, the Zomax package insert advised
ution in prescribing Zomax for long-term use, and recommended
inst use by children.
Zomax has been associated with a large number of reports of ana-
ylactoid reactions—allergic or hypersensitivity reactions which
erally involve rapid onset (i.e., within 20 minutes of taking the
ug), lowered blood pressure, breathing difficulty, swelling of the
e and/or other areas, rash, and itching. Patients going into ana-
ylactic shock can lose consciousness. Serious anaphylactoid reac-
ns require emergency room treatment with epinephrine (adrena-
), often accompanied by an antihistamine.
The first published report of a Zomax-associated anaphylactoid
action appeared in the April 16, 1981, issue of the *New England
ournal of Medicine*.[4] Dr. Judith Jones, formerly Director, FDA's
ivision of Drug Experience, testified that this report was probably
e agency's "first signal of a problem." [5]

Hearings before a Subcommittee of the Committee on Government Operations, House Representatives, "FDA's Regulation of Zomax," April 26 and 27, 1983, hereafter re-red to as Hearings.
[2] On May 3, 1977, McNeil requested permission, based on early Phase II clinical trial sults, to develop the drug as an analgesic rather than as a nonsteroidal anti-inflam-tory drug.
[3] Zomax is almost identical in chemical structure to Tolectin (generic name tolmetin tium), another nonsteroidal anti inflammatory drug manufactured by McNeil which s approved more than four years before Zomax.
[4] In subcommittee files. The case was reported by McNeil to FDA on March 18, 1981. is case report is in subcommittee files.
[5] **Hearings, page 418.**

On May 26, 1981, approximately seven months after Zomax was approved, FDA listed Zomax third among the drugs in its class in total number of reports received of drug-associated anaphylactoid reactions.[6] On July 23, 1981, McNeil added to the precautions section of the drug's package insert a statement that "[a]s with other nonsteroidal anti-inflammatory drugs, anaphylactoid reactions have been reported" for Zomax.[7]

On March 12, 1982, McNeil received its first report of a fatal Zomax-associated anaphylactoid reaction.[8] One week later, McNeil notified FDA that it was considering the dissemination of a Dear Doctor warning letter in light of an "increasing number of serious allergic and anaphylactic reactions" associated with Zomax.[9] On March 22 and 29, 1982, the company met with FDA to discuss the types of Zomax-associated anaphylactoid reactions which had occurred and to review McNeil drafts for such a letter.[10] On April 9, 1982, the company sent a Dear Doctor letter to over 200,000 physicians, urging caution in prescribing Zomax for patients who previously showed hypersensitivity to Zomax or any other nonsteroidal anti-inflammatory drugs, particularly aspirin and Tolectin (generic name tolmetin sodium), another McNeil drug nearly identical in chemical structure to Zomax.[11]

On February 8, 1983, McNeil reported a second death from Zomax-associated anaphylaxis.[12] At the company's request, FDA met with McNeil on February 11, 1983, to discuss development of new Zomax labeling. FDA recommended package insert revisions which would emphasize that patients restarting Zomax after a layoff period are at greater risk. At this meeting, the company informed FDA officials that it had received 908 reports of Zomax-associated allergic/anaphylactoid reactions.[13]

Following two additional reports of Zomax-associated deaths, McNeil and FDA met again on February 28, 1983. McNeil proposed at the meeting to promote Zomax primarily for chronic use, in view of the increased risk associated with intermittent use of Zomax.[14]

On March 3, 1983, a Syracuse, New York, television program featured a local physician, who recounted his life-threatening anaphylactoid reaction to Zomax.[15] In the wake of the publicity this generated,[16] McNeil announced on March 4, 1983, that it was temporarily removing the drug from the market, pending an evaluation of its

[6] Hearings, pages 277–280. Fourteen such reports had been made for Zomax, compared to 17 for Tolectin and 43 for Motrin (ibuprofen).
[7] The July 23, 1981, labeling supplement is in subcommittee files. The labeling change was immediately put into effect, although it was not formally approved by FDA until September 24, 1981.
[8] The report of this death is in subcommittee files.
[9] See memorandum by Dr. Marion Finkel, Associate Director for New Drug Evaluation, of a March 19, 1982, telephone conversation with Edward Lemanowicz of McNeil, which is in subcommittee files.
[10] Hearings, pages 108–9.
[11] Hearings, page 110.
[12] The report of this death is in subcommittee files.
[13] Hearings, page 126.
[14] Hearings, pages 116–7.
[15] The physician, Dr. Jack Yoffa, testified at the subcommittee's hearings.
[16] Dr. Robert Temple, Acting Director, FDA's Office of New Drug Evaluation, learned of the upcoming program during a March 3, 1983, telephone conversation, which is in Seay of McNeil. According to Dr. Temple's memorandum of that conversation, which is in subcommittee files, Dr. Seay "was a little worried about what everyone would say." In addition, an FDA memorandum of a March 4, 1983, meeting with McNeil states: "The Syracuse t.v. broadcast was discussed . . . both the firm and FDA had already been receiving calls from physicians, pharmacists, and consumers and many more were anticipated."

See Hearings p. 175.

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adverse effects and the development of new labeling. At the time of withdrawal, the company stated that a total of 5 deaths from Zomax-associated anaphylactoid reactions had been reported. Three of these deaths occurred in individuals who restarted the drug after a layoff period and were not allergic to aspirin. McNeil advised FDA shortly after removing Zomax from the market that 75% of the serious cases of allergic/anaphylactoid reactions reported for Zomax involved drug restarts.[17]

Following the Zomax withdrawal, McNeil proposed new labeling stating that "anaphylactic reactions, sometimes life threatening and rarely fatal, have been reported more frequently to Zomax than to other nonsteroidal anti-inflammatory drugs." The proposed labeling also emphasized that the majority of serious hypersensitivity reactions appear "to occur in individuals without a prior allergic history." [18]

On August 19, 1982, seven months before Zomax was removed from the market, FDA data from May 1981 showing 14 reports of Zomax-associated anaphylactoid reactions, were published in the *New England Journal of Medicine*.[19] In addition to this report, only five other reports of such reactions, involving a total of six cases, had been published in the medical literature prior to the drug's withdrawal from the market.[20] At the time of withdrawal, McNeil stated that it had received a total of 1,100 reports of Zomax-associated allergic/anaphylactoid reactions since the drug's approval.[21]

On April 26 and 27, 1983, the subcommittee held hearings on FDA's review and post-market regulation of Zomax. In addition, the subcommittee questioned FDA concerning the conditions which would have to be met before it would permit the drug's remarketing.

FDA referred the question of whether Zomax should be remarketed to its Arthritis Advisory Committee. On August 19, 1983, the advisory committee voted to recommend remarketing of Zomax on the condition that the sponsor conduct studies during remarketing to determine whether there is a population for whom Zomax, in view of its greater risks, could be shown superior to other drugs in its class.[22] The FDA has yet to act on the advisory committee's recommendation.

As of September 15, 1983, Zomax has been associated with a total of 2,161 reports of allergic/anaphylactoid reactions since its approval.[23] Based on McNeil adverse reaction reports, FDA has recently determined that Zomax-induced anaphylactoid reaction has probably caused nine or ten deaths in the United States since the drug's approval.[24] The FDA has also concluded that such a reaction cannot be ruled out as causing 28 other sudden, unexpected deaths. Some of these 28 deaths, however, occurred in patients with a history of cardiovascular disease. Too few details were available to classify the remaining portion as likely due to drug-induced anaphylactoid reaction.[25]

[17] Hearings, p. 175.
[18] In subcommittee files.
[19] Rossi, et al., "Tolmetin-Induced Anaphylactoid Reactions," *New England Journal of Medicine*, Vol. 3, No. 8 (August 19, 1982), pages 499–500.
[20] Samuel, "Apparent Anaphylactic Reaction to Zomepirac (Zomax), *New England Journal of Medicine*, Vol. 304, No. 16 (April 16, 1981), page 978; Smith, "Anaphylactic Shock, Acute Renal Failure, and Disseminated Intravascular Coagulation," *Journal of the American Medical Association*, Vol. 247, No. 8 (February 26, 1982), pages 1172–3; Ross, et al., "Near Fatal Bronchospasm Induced by Zomepirac Sodium," *Annals of Allergy*, Vol. 48, No. 4 (April 1982), pages 233–4; Corre and Rothstein, "Anaphylactic Reaction to Zomepirac," *Annals of Allergy*, Vol. 48, No. 5 (May 1982), pages 299–301; and Driver, et al., "Anaphylactic-like Reactions to Zomepirac," *Drug Intelligence and Clinical Pharmacy*, Vol. 16, Nos. 7–8 (July/August 1982), page 616.
[21] See March 4, 1983, McNeil press release, which is in subcommittee files.
[22] The verbatim transcript of the advisory committee meeting is in subcommittee files.
[23] This information is based on an October 4, 1983, McNeil submission to the Zomax

III. FDA Approved Zomax Without Sufficient Evidence That Its Benefits Outweighed Its Possible Carcinogenic Risk

Dr. Robert Temple, Acting Director, FDA's Office of New Drug Evaluation, testified that, based on animal studies, FDA believes Zomax has the "potential to . . . cause malignant tumors . . . in man." [26] FDA has held in the past that if a drug which has been found to be a carcinogen in animal studies has not been demonstrated superior to alternative drugs already on the market which do not have a carcinogenic potential, it is not "safe for use" within the meaning of the Food Drug, and Cosmetic Act.[27] The Committee finds that FDA failed to apply this standard in approving Zomax without the required evidence from adequate and well-controlled studies of its superiority to alternative drugs which are not potentially carcinogenic.

THE POTENTIAL CARCINOGENICITY OF ZOMAX

FDA's pharmacologist found up to a 30% incidence, or a three-fold increase, in adrenal medullary tumors in male rats fed Zomax in a two-year study.[28] The agency's statistician concluded that this evidence was statistically significant.[29] In addition, an FDA pathologist—the only agency reviewer to examine the rat tumor slides—diagnosed the tumors as "malignant." [30]

Based on his independent review of the report of this study, Dr. M. Adrian Gross, a former FDA toxicologist currently serving as a senior

[24] This analysis has been performed by Dr. John Harter, Group Leader for FDA's Zomax review, based on an October 7, 1983, adverse reaction submission from McNeil.
[25] *Ibid.*
[26] Hearings, page 115.
[27] Hearings, page 190.
[28] Hearings, page 146.
[29] Hearings, pages 156–7. The statistician's review was based on the tumor classifications of McNeil's pathologists. A consulting pathologist to McNeil found an even more significant trend in adrenal tumorigenicity in the rat study. See Hearings, pages 66 and 236–7.
[30] Hearings, pages 160–2. He diagnosed them as malignant pheochromocytoma tumors. Dr. Marion Finkel, formerly Associate Director for New Drug Evaluation, testified that the pathologist had "told us verbally that he felt that the tumors were not malignant." Hearings, page 163. However, no document in FDA's files contradicts his written conclusions as to their malignancy. In a May 10, 1983, letter to the subcommittee, the pathologist reiterated his diagnosis that the tumors were malignant and noted that he would have ensured that any change in diagnosis were documented as part of the agency's Zomax review record. Hearings, page 167.
On March 7, 1983, three days after McNeil withdrew Zomax from the market, FDA approved a February 4, 1982, proposed labeling revision which characterized the rat tumors as "benign". At an August 19, 1983, meeting of FDA's Arthritis Advisory Committee, Dr. Temple of the FDA stated, however, "I don't think we [FDA] would be prepared to say they are unequivocally benign." Transcript of advisory committee meeting page 60. In subcommittee files. Dr. Temple acknowledged before the subcommittee that some experts might characterize these tumors as exhibiting a "low order of malignancy." Hearings, p. 177.
Dr. M. Adrian Gross testified before the subcommittee that "It is the policy of the National Cancer Institute to regard all tumor-inducing agents as carcinogens" (Hearings page 93). He further testified that "there is no agent known that produces only benign tumors" and therefore to denote a drug as a 'tumorigen' is akin to using a misnomer." Hearings page 63. Similarly, Dr. Temple of the FDA acknowledged that a finding of "benign tumors in experimental animals "could represent some carcinogenic risk for man" (Hea

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ientific adviser with the Environmental Protection Agency, testified iat, correcting for surface area differences between rat and human, omax showed carcinogenic potential in rats at less than one-fifth of ie recommended human dose.[31] Since most carcinogens are identified i studies in which test animals are administered doses many times irger than the intended human dose, Dr. Gross testified that Zomax irried a "highly significant" human cancer risk.[32] Dr. Gross also found iat tumors appeared to occur earlier as the dose was increased, a phenomenon which constituted sufficient evidence of the drug's potential arcinogenicity.[33]

It is FDA policy that a positive carcinogenicity study must be reproducible," although "not [necessarily] at the same level of significance as the first study."[34] In this case, FDA has acknowledged hat a subsequent rat study, which showed a higher incidence of adenal tumors among treated male rats than controls, partially confirmed the results of the first study.[35] Although the trend, unlike that i the first study, was not statistically significant,[36] the rats were administered even less Zomax than those in the original study.[37]

[31] Page 65, Hearings. The rats were administered 4.15 percent to 17.70 percent of the ecommended human dose. Hearings, p. 38. Despite FDA's view that "there is no overriding ason to assume, in comparing doses administered to test animals with those recommended r humans, that extrapolation [from the test animal to the human] based on surface area any more reliable or precise" (Hearings, page 511) than extrapolation based on body eight (mg/kg), one of the most widely used toxicology texts presents a different view: One might also view dosage on the basis of weight as being not as appropriate as other ases, such as surface area. Such a dosage term would reduce interspecies variation and ven reduce variation in a single species where there is a wide variation in size, such s occurs in man." *Casarett and Doull's Toxicology*, ed. by J. Doull, C. D. Claasen, and . O. Amdur (McMillan Publishing Company, Inc.: New York, 1980), 2nd ed., page 22.

Even on a body-weight or mg/kg basis, the rats were administered one-half to threeurths the recommended human dose, according to FDA's pharmacologist, who found abeling approved by FDA stating that the rats were fed "approximately the human ose in mg/kg" to be "misleading". (Hearings, page 204.)

[32] Hearings, page 67.

[33] Hearings, page 65. The first death with tumor among the high-dosed rats occurred t day 406 in the two-year study, as compared to day 602 in the low-dosed group.

[34] Hearings, page 520.

[35] Hearings, 520. Following the subcommittee's hearings, FDA acknowledged a weak trend toward increased tumors" in the second Zomax rat study. Hearings, page 520. However, on March 7, 1983, three days following the drug's removal from the market, FDA pproved labeling stating there had been "no increase of tumors in males" in this study. n a similar vein, former Commissioner Hayes testified before the subcommittee that a reliminary report of this study showed no tumor increase. Hearings, page 93. However, he only review performed by FDA's pharmacologist of the second Zomax rat study, hich was based on this preliminary report, concluded that "tumor incidence was higher i all three treated groups than in controls. Probably the three treated groups combined ould give a significant difference against control." Hearings, page 197. Dr. Hayes implied that once the full report of the second Zomax rat study had been received and reiewed by the agency, FDA approved new labeling denying that tumors had increased in he study. Hearings, page 93. Dr. Temple of the FDA acknowledged before the subcomittee, however, that the only pharmacology review performed prior to approving this abeling revision was the one which identified an increased tumor incidence among treated ale rats. In fact, the full report of second rat study was never reviewed until shortly beore the agency was to appear before the subcommittee, and more than two years after DA received it. Hearings, page 93.

[36] The results of the second rat study are statistically significant if, as FDA suggested a connection with the results of a one-year Zomax monkey study, hyperplasia (or the abormal growth of normal cells) can be seen as a precursor lesion to neoplasia or tumors. Commissioner Hayes testified that the absence of hyperplasia in a one-year Zomax monkey tudy was evidence of the non-tumorigenicity of Zomax, Hearings, page 93.) If hyperplasia s a precursor to tumors, then the second rat study which, according to FDA, shows "total yperplasia and tumors were significantly increased" (Hearings, page 520) would reveal, ike the first Zomax rat trial, a statistically significant trend towards adrenal gland tuorigenicity. See Hearings, p. 60.

[37] Hearings, page 66. FDA testified that two eighteen-month Zomax mouse studies did ot show tumorigenicity. However, the animals in the higher dose mouse trial, according o Dr. Gross, were administered, on a body-surface basis, only .79 to 5.68 percent of the ecommended human dose, or a small fraction of the already small doses administered to he rats in the first Zomax rat study. Hearings, page 45. In addition, despite an FDAupported study showing that mice fed known carcinogens often take longer than 18 months o develop tumors (Hearings, page 212; see also memorandum of October 16, 1980 meeting. etween FDA and McNeil in Hearings, page 166), the agency did not implement its pharnacologist's recommendation to extend the mouse studies to 24 months. Hearings, pages 31 and 235.

Dr. Temple testified for FDA that Zomax "is and was considered a tumorigen"; [38] the rat tumor findings "could represent some degree of carcinogenic risk for man." [39] Dr. Temple, in fact, characterized the low doses at which Zomax induced tumors in the rat as "scary".[40]

FDA'S RISK/BENEFIT DETERMINATION

Before Zomax, FDA had never approved a nonsteroidal anti-inflammatory drug (NSAID) which it considered potentially carcinogenic. FDA's pharmacologist recommended nonapproval of Zomax, "pending resolution of whether adrenal medullary tumorigenicity and hyperplasia can or cannot be tolerated in a drug for which there are alternative therapeutic agents available." [41] While maintaining that it regarded the potential carcinogenicity of Zomax as a "serious matter," [42] the agency testified that evidence of the drug's unique effectiveness was "sufficient to support its approval . . . despite the tumorigenicity/hyperplasia in male rats." [43]

However, FDA has not determined from scientific evidence that Zomax is superior to alternative drugs which do not have a carcinogenic potential. Although he had previously questioned "the need for another analgesic [namely, Zomax] equal to aspirin with codeine or acetaminophen with codeine." [44] Dr. Robert Temple, Acting Director of FDA's Office of New Drug Evaluation, testified that some agency personnel believed Zomax was enormously valuable as a non-narcotic equivalent to and "potential replacement for modest doses of morphine." [45] The agency, however, has never approved claims of equiva-

[38] Hearings, page 159. FDA testified that the rat studies were inconclusive because "adrenal medullary tumors were of a type common in untreated rats." Hearings, page 92. Since a "tumorigen", as FDA acknowledges, is an agent which induces a significant increase in tumors in treated as compared to untreated animals (Hearings, page 516), it is immaterial if such tumors occur spontaneously in untreated rats. See Hearings, page 64. Moreover, the incidence with which such tumors occur spontaneously in rats appears to be a matter of scientific dispute. See Hearings, pages 58-60.

[39] Hearings, page 159. In acknowledging the carcinogenic risk of Zomax, Dr. Temple is stating FDA's institutional position, as well as the views of its reviewing pharmacologists. See Hearings, page 158. That Zomax may be carcinogenic is not, as Dr. Robert Gussin, Vice President for Scientific Affairs at McNeil, testified, the view of a lone agency "dissenter". Hearings, page 460.

Dr. Gussin also testified before the subcommittee that "the rat is a poor model with respect to prediction of the effect of zomepirac in man, since the rat metabolizes zomepirac sodium differently from man." At an August 19, 1983, meeting of the Arthritis Advisory Committee, Dr. Temple of the FDA did not find this argument persuasive, given the inherent limitations in testing for human carcinogenicity: "Everyone should be aware that there really are only two species typically used in cancer studies: rats and mice, and various strains of all of them, and it is unusual and very lucky if you have any reason to think the metabolism of the rat and the mouse for any drug is just like it is for humans. So to say that something is or is not a good model because it doesn't metabolize it exactly the same, that is just part of the basic facts of testing in rats and mice. That is often true. It may be true here also, but it is sort of ordinarily true as well." Verbatim transcript of August 19, 1983, Arthritis Advisory Committee meeting, pages II-58-59. In subcommittee files. Moreover, the Food, Drug, and Cosmetic Act places upon the sponsor of a new drug the burden for proving its product safe for marketing. That the rat might be, as McNeil maintains, a poor model for predicting human carcinogenicity, does not mean that McNeil has established the long term safety of Zomax. Moreover, as Dr. M. Adrian Gross testified, "[t]hese are the data that have been submitted as evidence of safety by McNeil" (Hearings, page 81) and the "least that we can state here is that none of these tests establish that Zomax is safe from a carcinogenic point of view." (Hearings, page 82.)

[40] Hearings, page 208. Despite such a characterization, FDA rejected the recommendation of its pharmacologist who, noting that Zomax had a "potential toxicity [i.e., carcinogenicity] not seen with other approved NSAIDs," recommended "a box warning in the labeling as a minimum . . . alerting to the carcinogenic and hyperplastic potential based on 2 yr rat study." Hearings, page 238.

[41] Hearings, page 238.

[42] Hearings, page 159.

[43] Hearings, page 88.

[44] Hearings, page 174.

[45] Hearings, page 176.

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nce to morphine as part of the Zomax labeling.[46] Both the supervisory edical officer in the Zomax review[47] and FDA's statisticians[48] do ot believe such an equivalence has been demonstrated. In approving omax, FDA excluded statements of such an equivalence from the rug's labeling, pending submission of results from an important study mparing the efficacy of Zomax and morphine.[49] Dr. John Harter, roup Leader in FDA's Zomax review, testified that the study eventuly proved to be "inconclusive." [50]

Dr. Temple of FDA's Office of New Drug Evaluation testified that omax was "uniquely effective compared to other nonsteroidal anti-flammatory drugs"[51] in treating higher levels of pain. Dr. Marion inkel, who preceded him in that position, acknowledged, however, iat the efficacy of the other NSAIDs had not been studied in similar ain levels. "[I]f they had been so studied," she testified, they "might so have been found to be as effective" as some considered Zomax to ".[52] Without clinical studies comparing the efficacy of Zomax to that other nonsteroidal anti-inflammatory agents for more severe pain, iere is no scientific basis for concluding that Zomax had been shown niquely effective" in treating such pain.

Dr. Temple of the FDA testified that "everyone . . . agrees" with ie assessment of Dr. John Harter, Group Leader for FDA's Zomax eview, that if Zomax had advantages over other NSAIDs, it was as a ain reliever for acute, not chronic use.[53] But chronic use, former Comissioner Hayes testified, would enhance the drug's carcinogenic risk. or that reason, he stated that Zomax was approved primarily for use a short-term analgesic.[54]

The Zomax package insert urged caution in prescribing the drug or chronic pain. Chronic use, however, was not contraindicated.[55] In ict, prior to approving Zomax, FDA expected that it would be used ironically. Because Zomax, like other anti-inflammatory drugs, had potential long-term uses," the agency's supervisory pharmacologist isisted that long-term studies be performed, notwithstanding that short-term analgesia is the [drug's] main indication."[56] The FDA ivision which regulates Zomax and the other NSAIDs had estabished a policy that all drugs with "anti-inflammatory properties," ncluding analgesic agents such as Zomax, "should meet the same . . . arcinogenicity requirements . . . This is because the likelihood is quite igh that they will be used . . . chronically" because of their anti-

[46] Hearings, page 189.
[47] Hearings, pages 180–1.
[48] Hearings, pges 183–8.
[49] Hearings, page 189.
[50] Hearings, page 190.
[51] Hearings, page 189.
[52] Hearings, page 191. Also see her October 7, 1980, memorandum at Hearings, page 2. At an August 19, 1983, meeting of FDA's Arthritis Advisory Committee, Dr. William aver of Georgetown University, a consulting expert to McNeil on the drug's analgesic operties, acknowledged this same point and mentioned a recent study which showed at Dolobid (generic name diflunisal) had actually peaked at the same level and provided nger relief in oral surgery pain than Zomax. See verbatim transcript of Arthritis Advisory mmittee, pages 11-35–6, in subcommittee files. This study appears in the medical literare. See Forbes, Butterworth, Burchfield, Beaver and Shackleford, "A 12-Hour Evaluation the Analgesic Efficacy of Diflunisal, Zomepirac Sodium, Aspirin, and Placebo in Postperative Oral Surgery Pain," *Pharmacotherapy*, Supplement 1, Vol. 3, No. 2 (March/April 983), pages 38S–46S. As discussed below, Dolobid (diflunisal) may be carcinogenic.
[53] Hearings, page 119.
[54] Hearings, page 92.
[55] Hearings, page 120.
[56] Hearings, page 519.

inflammatory properties.[57] FDA even allowed Zomax to be heavily promoted for chronic use,[58] and, according to FDA testimony before the subcommittee, approximately 20 percent of Zomax patients were chronic users.[59]

Because it now believes intermittent use of Zomax increases the risk of serious anaphylactoid reaction, McNeil has proposed "repositioning" the drug primarily for the relief of chronic rather than intermittent, acute pain.[60] Former Commissioner Hayes, however, testified before the subcommittee that FDA would have to "reconsider the implications" of the rat tumor findings before it could approve such a proposal.[61] Since FDA has always known that Zomax would often be used chronically, the Committee believes it would have been appropriate to "reconsider the implications" of the drug's carcinogenic potential prior to its approval. Since FDA has permitted the drug to be promoted for chronic use, and has acknowledged that a large percentage of Zomax patients were chronic users, the committee questions the agency's contention that it had taken the "tumorigenicity finding . . . seriously."[62]

The subcommittee's investigation also revealed that the FDA has approved several other drugs which have not been adequately tested for their cancer-causing potential. For example, the agency approved the nonsteroidal anti-inflammatory drug, Dolobid (generic name diflunisal), despite its possible association with lung (pulmonary adenomas) and liver (hepatocellular adenomas) tumors in male mice,[63] and despite deficiencies in the conduct of the two-year Dolobid mouse study which could have prevented the development of additional tumors and thereby masked a significant carcinogenic risk.[64] The sponsor agreed to conduct another such mouse study during the drug's marketing period.[65]

The FDA also approved the nonsteroidal anti-inflammatory drug, Oraflex (generic name benoxaprofen), even though low survival rates among treated rats in a two-year rat study—the only completed carcinogenicity study reported prior to the drug's approval—prevented meaningful statistical analysis.[66] FDA's pharmacologist concluded:

[57] Hearings, pages 137–9.
[58] See Hearings, pages 135–7. The subcommittee reviewed a Zomax advertisement which emphasized in bold-faced print the drug's usefulness for "chronic pain" such as "chronic osteoarthritis and musculoskeletal pain." Hearings, page 135–6. Despite Dr. Temple's statement that the advertisement presented an "unbalanced emphasis on the chronic uses" (Hearings, page 136), there is no record that FDA took any regulatory action against the sponsor in connection with this advertisement.
[59] Hearings, pages 105–6. The number of chronic users was estimated at 100,000 per month. Hearings, page 107.
[60] Hearings, page 90.
[61] *Ibid.*
[62] Hearings, page 511.
[63] Hearings, pages 409–11.
[64] Even though all 10 of the surviving high-dosed animals were sacrificed three months prior to the completion of the trial (at week 85), a statistically significant trend toward lung tumors almost developed. Noting that 6 of the 15 tumors in the mid-dosed group occurred between week 86 and 97, FDA's statistician concluded that:

> . . . the result of the lifetime oral carcinogenicity study in mice should be interpreted with utmost caution. The trend analysis is technically non-significant ($p=0.066$) after adjustment for a number of tumor sites. It is very near to statistical significance, however . . . Unfortunately, there is no way to obtain a better estimate. The killing of all the high dose animals at Week 85 might have masked the incidence of tumors in this group. The between group comparison shows that the incidence of lung adenomas in the medium dose male mice is significantly higher than that in the controls. Hearings, page 410.

[65] *Physicians' Desk Reference*, 37th ed., 1983, page 1290.
[66] Hearings, pages 405–6.

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"The two-year rat toxicity study does not support the safety of this drug for its chronic use in humans." [67] At the time of approval, the sponsor had undertaken a two-year mouse study and had submitted a protocol for a one-year rat study.[68]

In a similar vein, the FDA approved Feldene (generic name piroxicam), another nonsteroidal anti-inflammatory drug, even though its pharmacologist questioned whether 18-month studies in the rat and the mouse were of sufficient duration to establish the drug's long-term safety.[69] FDA informed the sponsor "that a commitment to do a [post-approval] 24 month animal study would be considered adequate for approvability and would not slow the approval process." [70]

Although he could not speak to the details of FDA's reviews of Dolobid, Oraflex, and Feldene, Dr. Temple of the FDA testified that before it would have approved these drugs the agency must have concluded that their carcinogenicity studies "were sufficient to rule out a major risk." [71] The observation that properly performed carcinogenicity studies might show a statistically significant association with lung cancer in mice [as with Dolobid] or the conclusion that "the safety of [Oraflex] for its chronic use in humans" has not been demonstrated, however, suggest that the agency has approved drugs without the data needed to "rule out a major risk." The committee notes, in this connection, that a number of nonsteroidal anti-inflammatory drugs under investigation have been shown to be potentially carcinogenic. Some of these drugs—including Clopirac,[72] Driftalone,[73] Rengasil,[74] and Cicloprofen [75]—were ultimately withdrawn by their sponsors from investigational drug testing. Others—among them ketoprofen,[76] Maxicam [77] and oxaprozin [78]—are still under FDA review.

The law requires FDA to ensure that new drugs are safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling before approving them for marketing. Unless the FDA, prior to approving a new drug, is able to conclude that its benefits outweigh any drug-related risk of cancer which may be found after it is marketed, the committee does not believe the agency can meet its statutory responsibility for protecting the public from potentially unsafe drugs when it approves a new drug which has not been adequately tested for its cancer-causing potential.

The committee questions whether FDA always performs a risk-to-benefit assessment before approving drugs which its experts do not believe have been shown safe for long-term use. For example, Dr. Robert Temple, Acting Director, FDA's Office of New Drug Evaluation, testified during the subcommittee's hearing on FDA's review of Feldene on August 4, 1982, that the data offered in support of the drug's effectiveness was considered "marginal" by "all parties" to that review.[79] Former Commissioner Hayes, in fact, acknowledged sharp disagreement within the agency as to whether the drug's effectiveness was supported by adequate and well controlled studies, as required by law.[80] Both the Group Leader for FDA's Feldene review and FDA's statistician believed such support had not been provided. With only "marginal" evidence of the drug's effectiveness, FDA approved Feldene, a drug for chronic use,[81] even though its reviewers questioned whether its long-term safety had been established. In view of the approval of this drug, the committee is concerned that FDA's drug approval process does not give sufficient consideration to the potential carcinogenicity of new drugs.

[67] Hearings, page 403.
[68] Hearings, page 407.
[69] Hearings, pages 389–90 and 392. On the inadequacy of 18 month mouse studies for determining carcinogenicity, see note 37 above.
[70] Hearings, page 392.
[71] Hearings, page 412.
[72] Clopirac has been associated with bladder and thyroid tumors in rats. Hearings, page 352.
[73] Driftalone has been associated with hepatocellular carcinomas in mice and rats. Hearings, pages 353–4.
[74] Rengasil has been associated with pancreatic adenomas in rats. Hearings, pages 358–60.
[75] Cicloprofen has been associated with liver tumors in mice. Hearings, pages 361–2.
[76] Ketoprofen has been associated with pituitary and mammary adenomas in rats. Hearings, page 366.
[77] Maxicam has been associated with renal transitional cell tumors in rats. Hearings, pages 533–7.
[78] Oxaprozin has been associated with testicular adenomas in rats. Hearings, page 545. Another arthritis drug, Ridaura (generic name auranofin), which is an oral gold compound rather than a nonsteroidal anti-inflammatory drug, has been associated with renal tubular neoplasia in a 12-month rat study. Hearings, page 378.

IV. FDA Monitoring of Zomax-Associated Adverse Reaction Reports Was Deficient

Former Commissioner Hayes testified before the subcommittee that "[t]racking adverse reactions has a very high priority" at the Food and Drug Administration.[82] In connection with HHS proposals to speed the approval of new drugs, in fact, both Dr. Hayes [83] and former HHS Secretary Richard S. Schweiker [84] have proposed measures purportedly designed to strengthen surveillance of adverse effects reported for marketed drugs.[85] Although the agency has stated that it has "taken several administrative steps to correct problems" previously encountered in "processing and analyzing" incoming adverse reaction reports for marketed drugs,[86] the subcommittee's investigation of the agency's regulation of Zomax revealed that agency monitoring of adverse reactions is still a serious problem.

Mr. Robert Eaton is responsible in FDA's Division of Drug Experience for monitoring incoming adverse reaction reports for Zomax and the other nonsteroidal anti-inflammatory drugs. He testified before the subcommittee that he was surprised when McNeil informed FDA officials on February 11, 1983, that it had submitted to the agency 908 reports of Zomax-associated anaphylactoid reactions since the drug's approval. Mr. Eaton had thought that FDA had only received approximately half that number of reports from the sponsor.[87] An FDA memorandum of a February 28, 1983, meeting with McNeil revealed that shortly before the drug was withdrawn from the market, the agency's computerized tracking system contained only 270 reports of Zomax-

[79] Hearings before a Subcommittee of the Committee on Government Operations, House of Representatives, "The Regulation of New Drugs by the Food and Drug Administration: The New Drug Review Process," August 3 and 4, 1982, page 439.
[80] *Ibid.*, pages 44–5.
[81] Feldene is indicated for the relief of the chronic pain and inflammation of arthritis.
[82] Hearings, page 128.
[83] Hearings before a Subcommittee of the Committee on Government Operations, "The Regulation of New Drugs by the Food and Drug Administration: The New Drug Review Process," August 3 and 4, 1982, page 25.
[84] HHS Fact Sheet, "New Drug Approval Reforms," June 23, 1982, page 3.
[85] Also see proposed revisions in the new drug approval process, 47 Fed. Reg. 46622, 46624 (October 19, 1982).
[86] *Ibid.*, page 46637.
[87] Hearings, page 127.

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ociated allergic/anaphylactoid reactions, compared to the more n 900 which McNeil apparently had submitted.[88]

The agency classified Zomax anaphylactoid reactions as "B" re-ts—that is, as reports of serious adverse effects already listed in drug's labeling.[89] Eighty-nine (89) percent of the "B" reports k 72 days or more to be entered into FDA's computerized tracking tem during the most recently reported quarter preceding the sub-mmittee's hearings. Added to these delays were the several weeks often took to classify such reactions once they were received by DA's Division of Drug Experience.[90]

Former Commissioner Hayes maintained, however, that timely ocessing of "B" reports was not the agency's highest priority. The ncy, he testified, attached the greatest importance to tracking "A" orts—those not previously associated with a drug and therefore not ed in its labeling: "I don't think the system keeps us from knowing ich are the serious or the unknown reactions . . . I think the track ord on that is rather good." [91] The subcommittee's investigation, wever, revealed that FDA did not process its high priority "A" re-rts in an efficient and effective manner. According to the most recent a available to the subcommittee at the time of its hearings, it took days or more—how much more FDA records do not specify—for agency to enter such reports into its computers once they had n classified.[92] In view of the agency's requirement that drug manu-turers report unexpected reactions within 15 days,[93] the committee ds such long processing delays both surprising and distressing.

The law requires FDA to determine whether a marketed drug con-nues to be safe under the conditions of use for which it was ap-oved [94] as well as to ensure that physicians are accurately informed rough product labeling of all important clinical experience with h a drug.[95] The agency cannot carry out these vital public health sponsibilities unless it efficiently and effectively manages its adverse action tracking and analysis system.

The committee notes that on March 8, 1982, more than a year before subcommittee hearings, the General Accounting Office issued a re-rt entitled, *FDA Can Further Improve Its Adverse Drug Reaction porting System*, which criticized FDA's Division of Drug Experi-e for taking an average of 3.3 months, and sometimes more than a ar, to enter adverse reaction reports into its computerized tracking stem.[96] The committee does not believe that the agency since this ort has instituted management reforms to establish and maintain comprehensive and current computerized file of adverse drug ex-riences into which new reports can be processed quickly." [97]

Former Commissioner Hayes minimized in his testimony before the committee the importance of tracking the numbers of incoming orts of Zomax-associated anaphylactoid reactions because the ug's association with such reactions had already been "signalled":

[88] Hearings, page 116.
[89] Hearings, page 127.
[90] Hearings, page 131.
Hearings, page 133.
Hearings, page 131.
[91] 21 C.F.R. § 310.300(b)(2).
[92] § 505(e) of the Food, Drug, and Cosmetic Act.
[93] § 502(a) of the Food, Drug, and Cosmetic Act.
[94] Hearings, page 132. GAO Publication No. HRD-82-37.
[95] 47 Fed. Reg. 46622, 46624 (October 19, 1982).

> Mr. WEISS. Let me suggest that both you and Dr. Meyer have now talked about a signal system. Right? I assume that the signal system is only as valid as the information which comes in to set the signals off.
>
> Dr. HAYES. We already had the signals. The important thing was not just keeping track of how many signals. The red flag was already up.[98]

However, one of the agency's principal adverse reaction "signalling method[s]," [99] the Surveillance of Adverse Reactions or SOAR method, depends on tracking the numbers as well as the kinds of adverse effects reported for marketed drugs. The SOAR method compares, for a particular time period, a drug's proportional share of a particular type of adverse reaction reported for its class with its class market share as reflected by numbers of prescriptions filled.[100] A drug which, compared to other drugs in its class, has attracted far more reports of a particular side effect than would be expected from its market share would strongly signal the need for further review.

In January 1981, for example, the agency completed a study using the SOAR method which concluded that Tolectin (generic name tolmetin sodium), a McNeil arthritis drug nearly identical in chemical structure to Zomax, might have a higher incidence of anaphylactoid reactions than other drugs in its class. Tolectin had 27 percent of the anaphylactoid reactions reported for its class while claiming only two percent of the class' market.[101]

No similar type of analysis was performed for Zomax,[102] even though Dr. John Harter, Group Leader for FDA's Zomax review, acknowledged that he began to suspect that Zomax was associated with a higher incidence of anaphylactoid reactions than other drugs in its class as early as May 1981. He based this suspicion on a May 26, 1981, agency report entitled, "A Comparison of Anaphylactoid Reactions Associated with Nonsteroidal Anti-Inflammatory Drugs," which, only seven months after Zomax was approved for marketing, listed the drug third among the NSAIDs in total number of reports of anaphylactoid reactions associated with it use.[103] Using the data in this report, the subcommittee staff confirmed, based on an analysis resembling the SOAR method, that Zomax may have already had a higher incidence of such reactions than all other drugs in its class, including Tolectin.[104] While Zomax had only 1.2 percent of the total life-time market for the drugs in its class (based on total numbers of prescriptions filled), it had already been associated with 13.6 percent of the total number of anaphylactoid reactions reported for that class.[105]

[98] Hearings, page 128.
[99] Hearings, page 267.
[100] The method assumes that, for any comparable time period, that the rate of non-reporting of adverse effects is evenly distributed across the drugs in a class.
[101] Hearings, pages 264 and 276.
[102] Hearings, page 276.
[103] Transcript of a June 20, 1983, taped interview with subcommittee staff, page 16, in subcommittee files. Mr. Robert Eaton of FDA's Division of Drug Experience similarly testified that he began to sense that Zomax was attracting more reports of anaphylactoid reactions than other drugs in its class in the fall of 1981. Hearings, page 124.
[104] Hearings, pages 281–2. Zomax was associated with 30 percent more reports of anaphylactoid reactions per million prescriptions than Tolectin.
[105] This calculation is based on the subcommittee staff analysis appearing at page 282 of the Hearings. It is based on total number of nonsteroidal anti-inflammatory drug prescriptions filled since the first NSAID was marketed in the United States and not on the number filled for the seven month period from the approval of Zomax to the May 26, 1981 report. A similar analysis based on prescription data for that period would show Zomax to have been associated with a substantially larger percentage of the anaphylactoid reactions reported for its class.

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Because Zomax has a virtually identical chemical structure to Tolectin, it is surprising that FDA never conducted a similar analysis.[106] In fact, while Tolectin was approved for use as an arthritis medication, of the 12 reports of Tolectin-associated anaphylactic reactions featured in an agency *ADR Highlights* published on June 20, 1979, approximately 16 months before Zomax was approved, occurred upon restarting the drug after a layoff period.[107] Since FDA knew that Zomax, unlike Tolectin, was to be used primarily for intermittent rather than chronic pain, it is particularly surprising that a SOAR or similar analysis of Zomax-associated anaphylactoid reactions was never performed.[108]

In testifying that implementation of the SOAR methodology was a "high priority" for her division,[109] Dr. Judith Jones, then the Director of FDA's Division of Drug Experience, informed the subcommittee that resource constraints were responsible for the agency's failure to conduct such an analysis; the SOAR methodology, she testified, "is fairly labor intensive."[110] The committee notes that the subcommittee staff analysis based on the agency's May 26, 1981, listing of anaphylactoid reactions reported for the nonsteroidal anti-inflammatory drugs took less than an hour to perform.

If resource constraints are preventing implementation of a "high priority" system for analyzing important safety information reported for marketed drugs, the committee believes the agency and the Department of Health and Human Services have an obligation to bring this matter to the attention of the Congress. The committee notes, in this connection, that FDA was unable to provide for the hearing record the estimated costs for widescale implementation of the SOAR methodology by its Division of Drug Experience.[111]

Former Commissioner Hayes has testified on the importance of strong post-market surveillance to detect rare adverse effects which are not likely to occur in clinical trials:

> An essential purpose of clinical testing of a drug before market approval is to detect adverse effects that are frequent and serious. However, detection of relatively rare adverse effects cannot and should not be a goal of premarket testing, because of the very large number of patients required. An adverse reaction with a frequency of 1 in 1,000 patients is considered uncommon, but if it is medically serious, it clearly assumes public health importance if the drug will be used by millions of people. The reporting of adverse events in patients who receive the drug after marketing is a useful way of detecting and determining the incidence of rare and infrequent adverse reactions. The monitoring of adverse reactions is well-accepted today as an essential scientific endeavor that complements the pre-marketing evaluation of a drug.[112]

[106] Since the drug's removal from the market, according to Dr. Judith Jones of FDA's Division of Drug Experience, FDA has undertaken such an analysis. Hearings, page 276.
[107] Hearings, page 341.
[108] Hearings, page 341.
[109] Hearings, page 288.
[110] Hearings, page 283.
[111] Hearings, page 289.
[112] Hearings before the Subcommittee on Natural Resources, Agriculture Research and Environment of the Committee on Science and Technology, U.S. House of Representatives, "Drug Lag," September 16, 1981, page 71.

While rigorous post-market surveillance is essential for protecting the public from the unexpected adverse effects of marketed drugs, the agency must ensure that it has obtained and made use of all available information on the safety of new drugs before approving them for marketing in the first place. The subcommittee's investigation of Zomax has revealed that FDA had received clinical trial reports of Zomax-associated anphylactoid reactions—purportedly a rare and unexpected reaction which only appeared subsequent to the approval of the drug—which had escaped the attention of the agency's reviewers prior to the drug's approval. Although the originally approved labeling for Zomax did not mention such reports,[113] and, according to Dr. Harry Meyer, Director, FDA's National Center for Drugs and Biologics, "nothing indicating anaphylactic hypersensitivity reactions" occurred in the premarket trials,[114] a board-certified allergist who reviewed Zomax clinical trial reports for the subcommittee identified anaphylactoid reactions among the drug-associated adverse effects submitted during the pre-market clinical trials. He characterized one of those reactions, involving a patient "with respiratory impairment requiring intensive treatment in a hospital emergency room," as "life threatening."[115] Despite the testimony of Dr. Robert Temple, Acting Director, FDA's Office of New Drug Evaluation, that the reaction did not appear "unusually severe,"[116] the agency later informed the subcommittee that this case qualified as "serious" according to FDA criteria.[117] The agency also acknowledged that this case "seems likely to have been a drug-related episode" and "a term such as bronchospasm, laryngeal edema, or asthma . . . could have been listed" in the drug's original labeling.[118] In view of the virtual chemical identity between Zomax and Tolectin, a drug suspected before Zomax was approved to have a high incidence of anaphylactoid reactions, the committee believes the agency did not exercise sufficient care in reviewing pre-market reports of Zomax-associated adverse effects.

In its recent report on "Deficiencies in FDA's Regulation of the New Drug 'Oraflex'," the committee similarly found that FDA reviewers failed to note several reports of serious Oraflex-associated liver and kidney disease prior to approving Oraflex for marketing. This proved particularly important in light of the numerous reports received of fatal and serious drug-associated liver and kidney injury after the approval of Oraflex.[119]

The committee appreciates the limitations of pre-market investigational drug trials in predicting the full range and severity of adverse reactions which will occur once a drug is marketed to a large population. At the same time, the committee believes FDA has a responsibil-

[113] FDA acknowledged that "the original Zomax labeling contained no warning regarding anaphylactoid reactions." Hearings, page 332.
[114] Hearings, page 284. McNeil similarly testified that "no anaphylactic reaction had occurred in those clinical trials." Hearings, page 462. See also March 4, 1983, McNeil press release in subcommittee files. As late as the August 19, 1983, meeting of FDA's Arthritis Advisory Committee, Dr. John Scarlett of McNeil stated that "no anaphylactoid reactions were observed during clinical trials prior to the approval of the drug for marketing." Verbatim transcript of meeting, page II-41, in subcommittee files. By the time the advisory committee met, Dr. Temple acknowledged that at least one case of possible "bronchospasm and something more severe" had been reported in the pre-market trials. Verbatim transcript, page II-71, in subcommittee files.
[115] Hearings, pages 299–300 and 322.
[116] Hearings, page 334.
[117] Hearings, page 332.
[118] Hearings, page 332.
[119] Report by the Committee on Government Operations, "Deficiencies in FDA's Regulation of the New Drug 'Oraflex'," H. Rep. No. 98-511, November 9, 1983, pages 9-11.

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prior to permitting marketing, to make use of all important safety ormation in its possession. While the FDA is expected to process drug applications as efficiently as its resources permit, the agency st not compromise the public protections intended by the law.

V. FDA Ignored Evidence Relating to the Risks of Zomax

Since Zomax was withdrawn from the market, McNeil has proposed narketing the drug with labeling emphasizing that a "majority" of -threatening and fatal anaphylactic reactions reported for the drug urred in "individuals without a prior allergic history." [120] As dis-sed above, the incidence of severe anaphylactoid reactions may have n higher for Zomax than for all other drugs in its class during most ts marketing life. The inability to predict from past medical history ich users are most susceptible to such reactions compounds the g's dangers. This has prompted some to suggest that the drug is safe for use. Dr. Kenneth Berneis, a family practitioner from inwell, Michigan, for example, expressed the opinion that the drug not be relabeled adequately to protect patients because "there is no y to predict who will react to the drug, either first occurrence or ondary use." [121]

Almost two years before the Zomax market withdrawal, FDA had dence suggesting that anaphylactoid reactions unpredictably oc-ring in patients without prior allergic histories had been reported more frequently for Zomax and its chemical analog, Tolectin, than other drugs in their class. The agency, however, never analyzed s evidence and, therefore, was never aware of the special danger in-ving the use of these almost chemically identical drugs.

Data which FDA published in its May 26, 1981, *ADR Highlights* itled, "A Comparison of Anaphylactoid Reactions Associated with nsteroidal Anti-Inflammatory Drugs," show that persons who ex-ienced anaphylactoid reactions to Zomax or Tolectin appeared far s likely to have had a previous anaphylactoid reaction to either of se drugs or to any other drug in their class than individuals who d experienced anaphylactoid reactions to other NSAIDs.[122] Only 9 percent of the individuals who had anaphylactoid reactions to max or Tolectin and who had previously taken other NSAIDs had perienced such reactions in the earlier exposure.[123] By contrast, over percent of the individuals who reacted to NSAIDs other than Zomax Tolectin and who had previously taken different NSAIDs had ex-ienced anaphylactoid reactions in the earlier exposure.[124] In addi-n, only 14.3 percent of patients having an anaphylactoid reaction to max or Tolectin who had earlier taken the same drug had previously

[119] This labeling is in subcommittee files.

[120] Hearings, page 15. Dr. Devra Davis, an epidemiologist and toxicologist associated a the Environmental Law Institute and Johns Hopkins University, who herself ex-ienced Zomax-induced anaphylactic shock, presented a similar view. Hearings, page 5.

[121] All the calculations which follow in support of this conclusion are based on Table 1 he *ADR Highlights*, page 280.

[122] Thirty-six (36) of the individuals who reacted to Zomax or Tolectin had been ex-ed to other NSAIDs. Five of those 36 reacted to other NSAIDs.

[123] Twenty-two of the individuals who reacted to a nonsteroidal anti-inflammatory drug er than Zomax or Tolectin had previously taken a different NSAID. Thirteen of these had earlier reacted to a different NSAID. Due to omissions in the entry of the aspirin a, it was not possible to calculate how many patients who had reacted to aspirin had viously taken and reacted to other NSAIDs.

reacted to it.[125] By comparison, 39.5 percent of the patients reacting to other NSAIDs who had previously taken the same drug had earlier reacted to it.[126] The May 1981 data show that it was significantly more difficult to predict serious hypersensitivity reactions to Zomax and Tolectin, based on prior allergic history, than to other nonsteroidal anti-inflammatory drugs.[127] These are the only data which FDA has generated which permitted such an analysis.[128]

Approximately 10 months after publication of these data, McNeil proposed a Dear Doctor letter which, in part, warned physicians of the risk of unpredictable anaphylactoid reaction to Zomax. In late March 1982, McNeil submitted for FDA response a draft Dear Doctor letter which included a warning concerning users who had no prior history of allergy to Zomax or other NSAIDs. Among the users whom the draft characterized "at higher risk of developing anaphylactoid reactions" were "patients with prior history of uneventful exposure [i.e. no prior hypersensitivity reactions] to Zomax or other nonsteroidal anti-inflammatory drugs" who used the drug "intermittently." The draft letter urged physicians to consider this warning "before represcribing Zomax." [129]

McNeil, however, failed to advise physicians of this risk in the Dear Doctor letter which it finally sent to over 200,000 physicians on April 9, 1982. Although it stated that "hypersensitivity upon re-exposure . . . cannot be ruled out" for patients who had previously had "mild reactions" to Zomax or other nonsteroidal anti-inflammatory drugs, it deleted the warning concerning individuals who had no prior history of allergy to Zomax or other drugs in its class.[130] Although Dr. John Harter, Group Leader for FDA's Zomax review, informed subcommittee staff that he thought the warning "was still going to be in [the April 9, 1982, Dear Doctor letter]," [131] he testified before the subcommittee that "[i]t was probably my determination" to delete it because in March of 1982 Zomax users without a prior allergy history did not appear to be at serious risk:

> I felt that of all the people who had developed anaphylaxis it was not those people who showed nothing on previous exposure. It is true that they had some risk, but more importantly the high risk people were the people who had any evidence of allergic reaction on previous exposure. A person who took it before and didn't have any problem at all is at lower risk.[132]

[125] Six of the 42 individuals reacting to Zomax or Tolectin who had previously taken these drugs had earlier reacted to the same drug. Of the individuals who reacted to Zomax or Tolectin, 73.7 percent (42 of 57 individuals) had taken them previously.

[126] Seventeen of the 43 individuals reacting to other NSAIDs who had previously taken the same drug had earlier reacted to that drug.

[127] The differences are, in fact, statistically significant.

[128] On November 3, 1983, several FDA personnel—among them Dr. John Harter and Dr. Vincent Kerusaitis, medical officers involved in the review of Zomax adverse reaction data, and Dr. Cheryl Graham of FDA's Division of Drug Experience—told subcommittee staff that FDA has not generated, and, to their knowledge, McNeil has not provided any other data on the percentage of individuals reacting to Zomax and the other NSAIDs who had previously reacted to the same drug or to another NSAID. On November 2, 1983, Mr. Robert Eaton of FDA's Division of Drug Experience, who assembled the data for the May 26, 1981, *ADR Highlight*, also informed staff that no such comparative analysis has been done since that report.

[129] Hearings, pages 108–9 and 111.

[130] Hearings, page 110.

[131] Interview with subcommittee staff on June 20, 1983, page 11.

[132] Hearings, page 111.

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Former Commissioner Hayes testified that a warning to physicians that prior allergic history is not predictive of a patient's susceptibility to life-threatening anaphylactoid reaction would have been misleading and contrary to the facts as then known:

> Do we have enough information to alert physicians that we know of some special problem here? That in fact was not the case. We did not have the data to tell that to a physician. As a physician I would have been misled . . . if I had been told that. I would have wanted to know what was known.[133]

The committee finds that the agency made no attempt to find out "what was known" about the nature of the risk of Zomax-associated anaphylactoid reaction at the time McNeil proposed to warn physicians that serious and sudden reaction to the drug may be unpredictable. Since May 1981, FDA has made no effort to collect data to compare the prior allergic histories of individuals experiencing anaphylactoid reactions to Zomax and the other NSAIDs. Furthermore, FDA never analyzed the May 1981 data which afforded such comparisons. As a result, the agency did not recognize that sudden and sometimes life-threatening reaction not only appeared to be more frequent with Zomax and Tolectin than other NSAIDs, but also substantially more difficult to predict and thereby avert.

Dr. Harter testified that in March 1982, Zomax users who had previously reacted to aspirin,[134] another NSAID, or mildly to Zomax were at greatest risk.[135] Following the subcommittee hearings, however, Dr. Harter recalled that the largest number of cases of Zomax-associated anaphylaxis which he reviewed in March of 1982 involved patients without a prior history of allergy to Zomax, aspirin, or other NSAIDs.[136] In view of this disclosure, the committee finds Dr. Harter's testimony that such patients were at lower risk surprising.

Dr. Harter maintained, however, that a warning concerning such patients was unnecessary because physicians should know from their

[133] Hearings, page 113.

[134] Dr. Harter testified that the recent death of an aspirin-sensitive patient was the "precipitating factor" for the meetings with McNeil to discuss the proposed Dear Doctor letter. Hearings, page 111. Documents in FDA's files, however, reveal that it was the recent increase in reports of serious hypersensitivity reactions to Zomax, not the death of an aspirin-sensitive patient, which led to those meetings. An FDA memorandum of the March 22 and 29, 1982, meetings with McNeil states: "Due to the recent increase in anaphylactoid reactions with Zomax, the sponsor is preparing a 'Dear Doctor' Letter." Hearings, page 108. In addition, a memorandum from Dr. Marion Finkel, then Associate Director for New Drug Evaluation, of a March 19, 1982, telephone conversation with Dr. Edward Lemanowicz of McNeil, stated that the firm was considering the dissemination of a Dear Doctor letter in light of an "increasing number of serious allergic and anaphylactic reactions" associated with Zomax. Memorandum in subcommittee files.

[135] Hearings, page 112.

[136] Transcript of taped interview with subcommittee staff on June 20, 1983, pages 12-3. In subcommittee files. In his testimony before the subcommittee, Dr. Harter recalled that in March 1982 he had classified approximately twelve reported Zomax-associated hypersensitivity reactions, in addition to one reported death in an aspirin-sensitive patient, as "anaphylactic" reactions. Hearings, page 111. He informed subcommittee staff that approximately half of these involved patients without a prior history of allergy to Zomax or other drugs in its class, with the other half fairly evenly divided between those who had previously reacted to aspirin and those to Zomax or other NSAIDs. Transcript of taped interview with subcommittee staff on June 20, 1983, pages 12-3. In subcommittee files. Unfortunately, the subcommittee staff did not have an opportunity to examine these twelve cases since, according to Dr. Harter, they were never aggregated as a group and inserted into FDA's files. *Ibid.*, page 12. In a November 3, 1983, telephone conversation, Dr. Harter emphasized that it was his "gestalt" recollection that half the reported cases involved patients without prior allergic histories to Zomax or other NSAIDs. He stated the percentage could have been larger. Staff memorandum of this conversation in subcommittee files.

medical training that this type of reaction was the "usual case with anaphylaxis."[137] However, the May 26, 1981, data—the only information FDA has assembled on the subject—suggest that this type of reaction is not the usual case with all nonsteroidal anti-inflammatory drugs and that, in fact, it was considerably more common with Zomax and Tolectin than with the other NSAIDs. Moreover, Dr. Harter has acknowledged that he had no data in March 1982 comparing the prior allergic histories of individuals experiencing anaphylactoid reactions to Zomax with those reacting to other NSAID.[138]

Up to the drug's withdrawal from the market on March 4, 1983, no warning about this type of reaction appeared in the Zomax package insert.[139] At the same time the contraindications section of the package insert has, since the drug's approval, warned that Zomax "should not be given to patients *in whom aspirin or other nonsteroidal anti-inflammatory drugs induce bronchospasm, rhinitis, or urticaria, or other hypersensitivity reactions*" (emphasis supplied).[140] FDA allowed McNeil to warn in a manner which, based on the May 1981 data, only protected a small fraction of Zomax patients at risk for serious anaphylactoid reaction.

Following the subcommittee hearings, Dr. Harter maintained that warning physicians about such a risk was futile:

> The problem with uneventful exposure is that you have no way to prevent the reaction by being alert. Let's suppose a patient had an uneventful exposure, comes into your office again and you—what can you do?[141]

FDA has the responsibility under law to ensure that drugs are safe under the conditions of use for which they were approved and that drug labeling clearly reflects their risk. FDA's failure to analyze the data it had collected prevented it from responsibly assessing whether the benefits of Zomax continued to outweigh the risk that physicians might be unable "to prevent" Zomax-induced anaphylactoid "reaction(s) by being alert."

During the subcommittee hearings, Dr. Harter testified:

> In any case, if I thought we were to the point where we needed to add [the warning in the April 9, 1982, Dear Doctor letter concerning Zomax patients without prior allergic histories to Zomax or other NSAIDs], I would have thought that we needed to change perhaps the indication portion of

[137] Transcript of taped interview with subcommittee staff on June 20, 1983, pages 14-5. If physicians need not be warned about what they already should know, the Committee questions whether the Dear Doctor letter, as Dr. Harter and other FDA witnesses testified, needed to warn physicians not to prescribe Zomax to aspirin-sensitive patients. In this connection, Dr. Daniel Ein, a board-certified allergist and an expert consultant to the subcommittee, described two cases of severe respiratory distress in aspirin-sensitive patients reacting to Zomax as belonging "to a group of patients that might have been expected to give adverse reactions to nonsteroidal anti-inflammatory drugs such as the zomepirac." Hearings, page 300. The advisability of not prescribing NSAIDs to aspirin-sensitive patients is frequently stated in the medical literature. See, for example, Spector and Farr, "Aspirin Idiosyncracy: Asthma and Urticaria," *Allergy Principles and Practice*, ed. Middleton (C. V. Mosehy Co.: St. Louis, 1983), page 1251.

[138] Staff memorandum of his November 3, 1983, phone conversation is in subcommittee files.

[139] The various versions of the Zomax labeling to March 4, 1983, is in subcommittee files.

[140] In subcommittee files.

[141] Transcript of taped interview with subcommittee staff on June 20, 1983, page 13.

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the label. This suggests that anybody is in danger again, and I think it would have required more extensive relabeling.[142]

When asked to explain this statement, Dr. Harter later stated:

> Second class drug thing. You know, that was in my mind and when we reached the point where I thought we should say, this drug has a higher incidence, enough higher that you have to worry about the uneventful exposure [problem] anymore than you usually do, then we ought to think about making this a second line drug.[143]

Although the agency had data which suggested the possibility that ou have to worry about the uneventful exposure [problem]" with omax more than "you usually do" with other drugs in its class, it was t until shortly before McNeil withdrew Zomax from the market on arch 4, 1983, that FDA recommended that the Zomax labeling state at the drug is "not for initial therapy but for those patients who do t get satisfactory relief from other NSAIDs [i.e., a second-line ug]." [144]

After it removed Zomax from the market, McNeil informed FDA at 75 percent of the serious cases of Zomax-associated anaphylactoid actions occurred upon restarting the drug after a layoff period.[145] cNeil currently believes that intermittent use of the drug is responble for the higher frequency of hypersensitivity reactions associated ith its use. Although FDA suspects that the increased risk of Zomaxduced hypersensitivity is related to the drug itself, it also feels it may related to the intermittent manner in which it has been used.[146]

However, not until a February 11, 1983, meeting, less than a month fore Zomax came off the market, did FDA recommend that McNeil arn about the possibly increased risk associated with intermittent use the drug: "It was recommended that McNeil consider stressing in ie labeling that there is greater risk for those patients restarting omax. This reaction is also seen to some extent in Tolectin." [147] Up to ie withdrawal of Zomax from the market on March 4, 1983, no menon of this risk appeared in the drug's labeling.[148]

Because of the drug's virtual identity to Tolectin, FDA apparently as aware long before February 11, 1983, of a potential problem ith intermittent use of Zomax. Dr. Robert Temple, Acting Director, DA's Office of New Drug Evaluation, acknowledged in his testiony before the subcommittee that FDA and the manufacturer were, ideed, aware of the risk accompanying intermittent use of Zomax as arly as March 1982:

> Mr. WEISS. Are you aware that the McNeil Co. advised FDA in March 1982 or perhaps earlier that there was a problem with intermittent use of Zomax?
>
> Dr. TEMPLE. We had that impression about Tolectin also some time around that time. So I don't believe that would be a surprise.[149]

[142] Hearings, page 114.
[143] Transcript of taped interview with subcommittee staff on June 20, 1983, page 26.
[144] See FDA memorandum of February 28, 1982 meeting with McNeil, Hearings, age 116.
[145] Hearings, page 175.
[146] Hearings, page 90.
[147] Hearings, page 126.
[148] The various versions of the Zomax labeling are in subcommittee files.
[149] Hearings, pages 107–8.

Since a majority of Tolectin-associated anaphylaxis featured in a June 20, 1979 FDA report involved intermittent use, as earlier discussed,[150] the committee believes that FDA did not require adequate warning of the risks associated with use of Zomax, a drug which, unlike Tolectin, FDA expected to be prescribed primarily for intermittent rather than chronic pain.

VI. FDA Improperly Referred the Question of Whether Zomax Should Be Remarketed to Its Arthritis Advisory Committee

FDA referred the question of whether Zomax should be remarketed to its Arthritis Advisory Committee. On August 19, 1983, almost four months after the subcommittee's hearings, the advisory committee voted to recommend the drug's remarketing.

During its testimony before the subcommittee FDA addressed the "conditions which must be met *before* Zomax may be remarketed" [151] (emphasis supplied). Former Commissioner Hayes testified that FDA "would have to conclude that there is a population of patients in whom the risks of [using Zomax] would be outweighed by its benefits" before the drug's remarketing would be permitted.[152] Commissioner Hayes also testified that because Zomax appeared to be associated with a higher risk of serious anaphylactoid reaction,[153] FDA would require, as a pre-condition for remarketing, that studies be performed to show that it relieved pain better than other drugs in its class:

> . . . there might be a population in which a relatively high risk might be acceptable, e.g., patients who cannot tolerate narcotics and who do not respond to non-narcotic analgesics. In this case, however, studies would be needed to determine whether other NSAIDs could function as well as zomepirac against narcotics. To date, these have not been done.[154]

In weighing the risks against the potential benefits of new drugs, FDA has established a policy which tolerates a "somewhat greater incidence of side effects" in a drug as compared to other drugs in its class "if those side effects are sufficiently offset by greater benefits." [155] The agency's explanation of the conditions which must be satisfied before Zomax may be remarketed was in keeping with this policy.

At the August 19, 1983, advisory committee meeting, FDA officials reiterated their belief that Zomax was associated with a higher incidence of anaphylactoid reactions than other drugs in its class.[156] Consistent with the agency's testimony before the subcommittee, Dr. Robert Temple, Acting Director, FDA's Office of New Drug Evalua-

[150] See discussion in Section IV above.
[151] See subcommittee's April 12, 1983, letter inviting FDA to appear for testimony, in subcommittee files.
[152] Hearings, page 95.
[153] Hearings, page 95.
[154] Hearings, page 90.
[155] 47 Fed. Reg. 22550 (May 25, 1982).
[156] After Dr. John Scarlett of McNeil presented Medicaid data (from the Computerized On-Line Medicaid Pharmaceutical Analysis and Surveillance System [COMPASS]), to the advisory committee showing that the risk of Zomax-associated anaphylactoid reactions was 2.55 higher than that for the other NSAIDs, Dr. Robert Temple of the FDA stated that, because of the manner in which these data were generated, he believed it was "amazing that you see any difference at all" and "impressive" that any statistically significant, "real difference" was found. Transcript of the August 19, 1983, Arthritis Advisory Committee meeting, pages 121–2, in subcommittee files. Dr. Judith Jones, then Director, FDA's Division of Drug Experience, also expressed the opinion that Zomax was associated with a higher risk of such reactions than other drugs in its class. *Ibid.*, pages 109–110.

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tion, emphasized at the outset of that meeting the need to "identify a real patient population . . . in fact, as opposed to in theory" who only respond to Zomax.[157] McNeil's chief expert at the meeting on the efficacy of Zomax, Dr. William Beaver of Georgetown University, acknowledged that such a population *could not be identified:*

> The question, can we identify a priori the kinds of patients who would do better on this drug than, say, some other nonsteroidal? Well, no. That's the problem.[158]

In an October 6, 1983, letter to the subcommittee, FDA could not cite any data from adequate and well controlled studies that had been provided to the Arthritis Advisory Committee "to enable the identification of a patient population for which Zomax was the nonsteroidal anti-inflammatory drug of choice."[159] At the time it referred the remarketing question to the advisory committee, FDA was not in possession of the scientific evidence it had earlier testified would be necessary to consider this question. Not surprisingly, in voting to recommend remarketing, the advisory committee was unable to identify a patient population for whom Zomax had proven superior to other drugs in its class.[160] In fact, the advisory committee conditioned its recommendation on the sponsor's undertaking studies during the drug's remarketing to define and prove the existence of such a population.[161] FDA had testified, however, that this should have been a *pre-condition* for remarketing Zomax.

Maintaining that the increased risk of serious anaphylactoid reaction resulted from the drug's intermittent use, McNeil presented at

[157] *Ibid.*, page 8.

[158] *Ibid.*, page 30.

[159] Hearings, page 531. On September 15, 1983, the subcommittee asked FDA whether such data had been provided the advisory committee. Hearings, page 530. The agency's October 6, 1983, response indirectly answered in the negative. The agency stated that the advisory committee had been provided "data from well-controlled studies . . . showing Zomax as effective" as narcotic regimens such as morphine, but did not directly answer whether data proving the existence of a patient population for whom Zomax had been shown *superior* to other NSAIDs had been given the advisory committee. Aside from data showing Zomax's equivalence to some narcotic regimens, FDA stated that "no additional data from adequate and well-controlled studies were provided the [advisory] committee regarding patient population identification." Hearings, page 531. The committee interprets this to mean that the advisory committee was not presented data identifying a patient population for whom Zomax had been shown better than other NSAIDs.

The committee also notes that at the advisory committee meeting Dr. John Harter, Group Leader for FDA's Zomax review, stated that the "pivotal evidence" for Zomax's equivalence to narcotics such as morphine was "missing" because of methodological problems in several Zomax-narcotics comparison studies. Transcript of the Arthritis Advisory Committee meeting, page 149. In subcommittee files. Contrary to the impression conveyed by FDA's October 6, 1983, letter to the subcommittee, the agency's reviewers had not concluded that "data from well-controlled studies . . . showing Zomax as effective" as narcotic regimens such as morphine had been supplied the advisory committee.

[160] Acting advisory committee chairperson Carol Dorsch summarized the advisory committee's consensus as follows: "Is there a population of patients for whom Zomax should be available and, secondly, has that patient population been defined? That is, do we need additional data, and I think we have said that we do, in order to define that population. I think we have answered affirmatively to both of those questions." Transcript of advisory committee meeting, page 195.

[161] Dr. John Harter, Group Leader for FDA's Zomax review, wrote in an August 22, 1983, memorandum summarizing the advisory committee meeting: "The committee also recommended that remarketing be contingent on the sponsor's commitment to undertake phase IV (post-remarketing) studies to prove that there is a subset of patients who respond to zomepirac and not to other nonsteroidal anti-inflammatory drugs." In subcommittee files. In view of Dr. Dorsch's (see footnote 164) and Dr. Harter's summaries, the committee questions the agency's statement in an October 6, 1983, letter to the subcommittee that "The [Advisory] Committee felt such a population could be identified, namely, patients unresponsive to other agents. The [Advisory] Committee did not believe it was necessary to carry out specific trials in a population unresponsive to other agents to conclude that such a population exists and would benefit from the drug." Hearings, page 534.

Moreover, in the absence of scientific evidence that such a class of patients exists, the committee does not believe "patients unresponsive to other agents" identifies a patient

the advisory committee meeting its proposal to "reposition" Zomax for the relief of chronic pain, particularly "intractable pain, such as cancer pain."[162] The committee believes that FDA also lacked the scientific evidence needed to request advisory committee consideration of this proposal.

McNeil first advanced its "repositioning" proposal prior to the subcommittee's hearings.[163] Former Commissioner Hayes testified before the subcommittee that the increased frequency of severe Zomax-associated hypersensitivity reactions might be "related to the drug itself rather than its intermittent use, and that, as a result, "it would be difficult to prove in advance" that "repositioning" Zomax for chronic use would appreciably lower the risk of those reactions.[164] Dr. Temple testified that before permitting Zomax to be remarketed for chronic use one

> . . . would have to conclude . . . that the risk of anaphylaxis would not be so severe where the drug is given chronically. As the testimony says, it is not clear how you would reach that conclusion.[165]

In her presentation four months later before the Arthritis Advisory Committee, Dr. Judith Jones, then the Director of FDA's Division of Drug Experience, stated that the

> . . . question as to whether or not [the increased risk of anaphylactic reaction] relates to a chemical difference or . . . to a type of use is still unresolved. . . . It is my opinion that the critical analysis that needs to be done and has not yet been done in either of our studies is whether or not repeated intermittent exposure in fact increases the risk considerably. . . .[166]

It is apparent that FDA did not have the data needed to conclude that chronic use would substantially reduce the risk of severe Zomax-induced hypersensitivity reactions when it permitted McNeil to present its remarketing proposal to the advisory committee. The committee, therefore, questions FDA's basis for bringing this proposal to the Arthritis Advisory Committee.

In connection with McNeil's proposal to "reposition" Zomax for the treatment of chronic pain, former Commissioner Hayes testified during the subcommittee hearings that Zomax "seems to have no advantage in chronic use over aspirin or other NSAIDs."[167] Elaborating on this testimony, Dr. Temple informed the subcommittee that such an advantage would have to be demonstrated before FDA "would even consider" McNeil's remarketing proposal.[168] Dr. William Beaver of Georgetown University, McNeil's own expert consultant, acknow

[162] See statement of Dr. Patricia Stewart of McNeil, verbatim transcript of advisory committee meeting, pages 74–5, in subcommittee files.

[163] See Hearings, page 116.

[164] Hearings, page 90. FDA cited the high hypersensitivity reaction rate associated with Tolectin, a drug almost chemically identical to Zomax, as evidence for the possibility that Zomax-associated hypersensitivity reactions are related to the drug rather than its intermittent use. Hearings, page 90.

[165] Hearings, page 97.

[166] Transcripts of August 19, 1983, meeting of the Arthritis Advisory Committee, pages 110 and 118, which is in subcommittee files.

[167] Hearings, pages 95–6.

[168] Hearings, page 99.

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edged at the advisory committee meeting that "there are no nose to nose comparisons of Zomax with the other nonsteroidals in, say, cancer pain or other chronic pain problems, as far as I know, that are even ongoing or have been done." [169] Consequently, Dr. Beaver acknowledged a "lack of data" comparing the efficacy of Zomax to other drugs in its class in treating chronic pain.[170] The advisory committee recommended studies to provide such data while the drug was being remarketed.[171] FDA had earlier testified, however, that these studies would have to be completed before remarketing of Zomax would be permitted.

Former Commissioner Hayes also testified that " it would be necessary to reconsider the implications" of the rat tumor findings before permitting Zomax to be remarketed for chronic use.[172] Prior to approving such remarketing, Dr. Temple testified, the agency would:

> . . . have to conclude something new and different about the risk of tumorigenicity. If all one were able to say is that the drug is another nonsteroidal anti-inflammatory drug with no advantage over other similar agents, it is obvious that making it available for chronic use would not be consistent with the attitude toward the tumorigenicity finding in the first place.[173]

Despite such testimony, and FDA's acknowledgement in an October 6, 1983, letter to the subcommittee that it had received no new "tumorigenicity information since the subcommittee hearings" to support the drug's chronic use,[174] the agency submitted McNeil's remarketing proposal to the advisory committee. Moreover, the agency had not altered its view of the meaning and significance of the drug's tumorigenicity between the time of the subcommittee's hearings and the August 19, 1983, meeting of the Arthritis Advisory Committee. In this connection, Dr. Temple informed the advisory committee:

> Now, on the other hand, I think our position as to what it all means is very much what it was at the beginning, that [the animal tumorigenicity of Zomax] is certainly something that needs to be considered if one is contemplating long-term exposure. . . . We . . . have not changed our view from what the initial label stated as their [the rat tumors'] significance.[175]

Since FDA had not "conclude[d] something new and different about the risk of tumorigenicity" by the time the advisory committee met, the committee does not believe the agency had sufficient scientific evidence to refer the remarketing issue to the advisory committee.

Dr. Temple summarized FDA's position on remarketing Zomax for chronic use when he testified before the subcommittee:

> . . . there would have to be substantial new information, information not now available, before one would reach a conclusion that making the drug available for chronic use is the right thing to do.[176]

[169] Verbatim transcript of advisory committee meeting, page 38, in subcommittee files.
[170] *Ibid.*, page 25.
[171] Transcript of advisory committee meeting, page 173, in subcommittee files.
[172] Hearings, page 96.
[173] Hearings, page 97.
[174] Hearings, page 532.
[175] Verbatim transcript of the Advisory Committee meeting, pages 59-60, in subcom-

There is simply no evidence that any "substantial new information" was available to FDA that justified referring the remarketing question to the Arthritis Advisory Committee. The committee must question FDA's motivation for bringing the matter before the advisory committee.

The committee believes that FDA wastes public funds and imposes on the time of busy professional consultants in convening advisory committees to consider alternatives unsupported by the required scientific evidence. In this connection, the committee stated in its 1976 report on the *Use of Advisory Committees by the Food and Drug Administration:*

> Utilization of an advisory committee is not essential if the agency itself has the capability to resolve the issue that is to be presented to a committee . . . FDA has made and is making nonessential use of advisory committees in dealing with issues that are well within the competence and expertise of its staff.[177]

The committee recommended in the report that the "waste[ful]" and "non-essential use of advisory committees" be eliminated and that "FDA place primary reliance on the use of its own staff resources to carry out its responsibilities and use advisory committees only in exceptional circumstances involving difficult medical or scientific issues where outside expertise is clearly required." [178] The Committee reiterates its recommendation that FDA refrain from the wasteful and unnecessary use of advisory committees.

A review of the verbatim transcript of the August 19, 1983, Arthritis Advisory Committee meeting reveals that FDA failed to inform the advisory committee members of its position as presented to the Congress that a patient population in whom the benefits of Zomax have been shown to outweigh its risk must be identified *before* Zomax may be remarketed. [179] The committee's 1976 report, in this connection observed that "advisory committees were asked [by FDA] at times to make decisions based on inadequate information." [180] The Committee believes FDA again acted improperly in failing to inform the advisory committee of the remarketing conditions which the agency had already established. In addition to withholding important information from the advisory committee, FDA presented options to the advisory committee inconsistent with its testimony before the subcommittee. For example, FDA asked the advisory committee to decide whether "a patient population [has] been adequately identified for which Zomax should be available *as either a therapeutic alternative* or as the drug of

[177] Report by the Committee on Government Operations, "Use of Advisory Committees by the Food and Drug Administration," 94th Congress, 2d Sess., H. Rep. No. 94-787, January 26, 1976, page 5.
[178] *Ibid.*, page 12.
[179] On September 15, 1983, the subcommittee asked FDA whether it had informed the advisory committee of "its position that a 'population of patients in whom the risk of it [Zomax's] use would be outweighed by its benefits' must be identified *before* Zomax may be remarketed?" The agency's October 6, 1983, response stated that identification of such a population "was the principal issue the Committee had to address," but neglected to answer whether it had told the advisory committee, as it had testified before the subcommittee, that remarketing would not be permitted *before* such a population were identified. See Hearings, page 531.
[180] Report by the Committee on Government Operations, "Use of Advisory Committees by the Food and Drug Administration," page 88.

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choice for that group?" [181] (emphasis supplied) FDA testified during the subcommittee hearings, however, that remarketing would be contingent on identifying a population for whom Zomax was the "drug of choice," not merely a "therapeutic alternative."

FDA unequivocally testified before the subcommittee that additional information would be needed *before* remarketing would be permitted. FDA then asked the advisory committee to consider whether "additional studies . . . should be done as a condition for remarketing Zomax" and, if so, "whether they should be done prior to *or concurrently with* remarketing?" [182] (emphasis supplied) The committee believes FDA acted inappropriately in providing the advisory committee options which were in conflict with determinations which the agency had already made. In this connection, the committee repeats its 1976 recommendation that FDA "terminate the practice of seeking recommendations from advisory committees on matters that have already been decided." [183]

Dr. John Harter, the supervisory medical officer for FDA's Zomax review and an agency witness before the subcommittee, in fact, recommended to the advisory committee that it support the drug's remarketing under conditions which were inconsistent with FDA's established position. He recommended that all required studies be performed in "Phase IV"—that is, *after* the drug has been allowed to return to the market:

> The real question in my mind is whether it should be done prior to approval or whether this should be one of the conditions of approval, that these studies be done as a Phase IV thing. I think that was really the intent of question four, is to try to decide the timing, because if you do it premarketing, you have—in the interim, you have to continue to supply the drug to those people who think on a compassionate basis that you should have it, which is a burdensome thing for both us and the sponsor, and you don't know how long that period is going to be, because as any of you who have tried to set up new methods know, you may think it is going to take you three months, and it takes you three years, and it is a very hard thing to know how quickly you can do that.
>
> So my recommendation would be that that would be a Phase IV thing.[184]

The committee believes it improper for FDA staff to urge advisory committees to adopt recommendations which do not meet the scientific requirements already established by the agency.

In recommending the remarketing of Zomax before a patient population for the drug has been identified, Dr. Harter did acknowledge a "problem":

> I think part of the problem . . . is, if you answer . . . no, has a patient population been adequately identified, and you have to do the study to identify it, how are you going to market it in the meantime, who are you going to market it for in the meantime? That is one of the problems.[185]

Dr. Harter further stated at the advisory committee meeting that if after remarketing, clinical studies are unable to identify a population for whom Zomax is superior to all other NSAIDs, then "it would again be a candidate to be taken off the market." [186]

The law requires that FDA conclude that a drug is safe and effective *before* it approves it for marketing. The committee questions the commitment of agency personnel to meeting their legal responsibilities in urging that market approval of a drug be conditioned on the promise that future studies *might* identify a population for whom the drug could be safely and effectively prescribed.

VII. Recommendations

The committee recommends that the Secretary of Health and Human Services take prompt action to correct the deficiencies identified in this report. The committee specifically recommends that:

1. In order to protect the public from unnecessary exposure to potentially carcinogenic drugs, FDA should:

   (a) Establish policies and procedures governing the approval of new drugs found to be carcinogens in animal studies. The committee recommends that FDA not approve new drugs which are potentially carcinogenic unless they are shown to have substantial advantages over alternative drugs on the market and are intended for the treatment of serious conditions.

   (b) Ensure that new drugs that have not yet been adequately evaluated for their carcinogenic potential only be approved in exceptional circumstances where they have been demonstrated to offer unique and essential benefits.

2. FDA establish procedures for prompt processing, review, and analysis of all adverse drug reaction reports for marketed drugs. The committee recommends that FDA insure that it has the resources needed to implement the best available methods for evaluating adverse drug reaction reports.

3. FDA use advisory committees only in exceptional circumstances involving technical medical or scientific issues where outside expertise is clearly required. The committee specifically recommends that steps be taken to:

   (a) Assure that FDA only seek advisory committee recommendations on specific issues which have not already been decided by agency personnel.

   (b) Assure that advisory committees are fully informed of all matters bearing on their deliberations.

   (c) Assure that FDA does not present options to advisory committees which are not consistent with the requirements of the Food, Drug, and Cosmetic Act.

[181] The questions for discussion which were submitted in advance to the advisory committee members are in subcommittee files.

[182] *Ibid.*

[183] Report by the Committee on Government Operations, "Use of Advisory Committees by the Food and Drug Administration," page 12.

[184] Transcript of advisory committee meeting, page 145, in subcommittee files.

[185] *Ibid.*, page 203.

[186] Transcript of Advisory Committee meeting, page 206, in subcommittee files.

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ADDITIONAL AND DISSENTING VIEWS OF HON. BUDDY MacKAY

The Subcommittee's investigation essentially dealt with two questions:

1. Did the FDA properly monitor adverse reaction reports associated with the use of Zomax?

2. Did the FDA properly carry out its statutory duties in approving Zomax?

In my view, the hearings of the Subcommittee established that the FDA monitoring of Zomax-associated adverse reaction reports was deficient. Thus, I am in accord with Section IV of the Report. I view Section V of the Report as cumulative, and believe it should have been included with Section IV. I do not believe the testimony established that FDA *ignored* evidence, but that the monitoring of adverse reaction reports was so inadequate that the evidence relating to risks associated with Zomax did not come to FDA's attention on a timely basis.

On the second question, I do not believe the testimony supports the conclusion that FDA approved Zomax improperly given the evidence that it is a possible carcinogen. This is not intended to in any way question the scientific determination that the drug is a tumorigen. The evidence suggests that it is. However, the FDA considered that evidence in its approval of Zomax and concluded that the benefits of Zomax outweighed the risks. While we personally may have reached a different conclusion, I do not believe we can properly report that the FDA acted improperly simply because we may disagree with the decision.

Because I believe the Committee and the Congress must be able to have complete faith in FDA's approval procedures, and because I believe the hearings were inconclusive on this point, I dissent from Section III, and respectfully suggest that further hearings should be held on those procedures in order that a proper conclusion can be reached.

BUDDY MacKAY.

ADDITIONAL VIEWS OF HON. EDOLPHUS TOWNS

In my view, the testimony does not support the conclusion tha the FDA approved Zomax without determining that its benefits out weighed its possible carcinogenic risk. The testimony is inconclusiv on that point. The prepared statements are not directed to that issue Accordingly, I cannot support Section III of the report and wish t have it reconsidered. Therefore, I respectfully suggest that additiona hearings be held that would receive evidence from all concerned partie and would be focused on two questions:

1) was the conflicting evidence of tumorigenicity in one sex of on specie of rats and the related issue of whether it presents a significan risk of carcinogenicity in man properly reviewed; and 2) has the FDA properly reviewed the issue of whether Zomax can be re-positioned fo use by a very restricted patient population that is characterized b serious, intractable or chronic pain and or whom there is no acceptabl alternative?

EDOLPHUS TOWNS.

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ADDITIONAL VIEWS OF HON. BEN ERDREICH

I share the subcommittee's findings relative to the lack of full attention by the FDA to cases involving adverse reactions to Zomax. However, I am concerned over the findings on the carcinogenic risk of the drug, for I feel that the results of the testimony are inconclusive. This inconclusive testimony, and conflicting reports that have been added to this record, present a case for further study, including the possibility of additional hearings by this subcommittee.

BEN ERDREICH

DISSENTING VIEWS OF HON. ROBERT S. WALKER, HON. JOHN N. ERLENBORN, HON. THOMAS N. KINDNESS, HON. LYLE WILLIAMS, HON. JUDD GREGG, HON. TOM LEWIS, HON. ALFRED A. (AL) McCANDLESS, AND HON. LARRY E. CRAIG

The federal Food and Drug Administration (FDA) has an awesome and vital task in ensuring that safe, efficient drugs are provided promptly to the American public. The Committee's responsibility in overseeing FDA is equally vital in promoting the health and well-being of all Americans.

Because of the importance of FDA's mission and the Committee's oversight function, we are especially sensitive to the conclusion and recommendations of our reports. We must strive to be as accurate as possible, and we must avoid generalizations that can lead to hasty conclusions, harm reputations or unnecessarily cause public alarm.

It is our belief that this report is misleading and likely to create impressions that are inaccurate. For this reason we offer these dissenting views.

We cannot agree with the finding that FDA approved Zomax without requiring a showing that its benefits outweighed its carcinogenic risk. FDA Commissioner, Dr. Arthur Hull Hayes, Jr., offered detailed testimony to the Subcommittee that refutes this finding. In his remarks, Dr. Hayes observed that animal studies showing possible tumors were not considered ominous, at least in short-term use, but the studies were cited in labeling precautions as reasons for caution in long-term use of Zomax.

It is important to note that reputable scientists differ as to the potential carcinogenesis of tumors discovered in Zomax studies. The Committee report does not acknowledge plainly this debate and, in fact, treats the issue as if carcinogenesis was a readily accepted conclusion.

Also not appropriately acknowledged is the FDA's response to the Subcommittee testimony of Dr. Adrian Gross. We feel the added perspective this response provides would be very valuable in clarifying the record.

At this point, we question the finding that FDA ignored evidence relating to other risks associated with Zomax. Evidence to support this conclusion is not compelling. We are aware of differences of opinion about the drug's risk but that is far different than a deliberate effort to ignore facts.

We reject the report's finding that "FDA improperly referred the question of whether Zomax should be remarketed to its Arthritis Advisory Committee." This subject was not discussed during the Subcommittee's hearings. FDA officials have not been heard on the subject

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and testimony of other interested parties is non-existent. FDA's referral of Zomax remarketing to its Arthritis Advisory Committee might deserve a hearing on its own merits or it could be included in an overall hearing on FDA's use of its many advisory committees. To include this finding and the accompanying recommendation, with the declaration of impropriety, is wrong.

The recommendations offered in the report require some review and some clarification. First, the report recommends establishing procedures and policies governing approval of new drugs found to be carcinogens in animal studies. We believe FDA has had such procedures for quite some time and that the agency does not approve such drugs unless the benefit of such drugs outweighs the risks to the recipient patient population.

The recommendation that new drugs that have not been adequately evaluated for their carcinogenic potential only be approved in exceptional circumstances is baffling. Animal studies are not required for every drug prior to approval. While we would agree that such studies should be required for drugs to be used chronically, we would be concerned that the mandatory animal testing for every drug would result in seriously delaying the approval of vitally important new drugs.

ROBERT S. WALKER.
JOHN N. ERLENBORN.
THOMAS N. KINDNESS.
LYLE WILLIAMS.
JUDD GREGG.
TOM LEWIS.
ALFRED A. (AL) MCCANDLESS.
LARRY E. CRAIG.

ADDITIONAL VIEWS OF HON. TED WEISS

It is the subcommittee's function to see that the Food and Drug Administration and other Federal agencies subject to its jurisdiction properly enforce the laws they administer. In concluding that FDA, in its regulation of Zomax, did not meet its statutory responsibility for protecting the public's health and safety, this report very carefully analyzes and evaluates the subcommittee's extensive hearing record and related documents. I believe the report is both reliable and constructive.

The dissenting views of some of my colleagues, which appear to defend the FDA even when its actions have deprived the public of the health protections intended by the Congress seem, therefore, to be misplaced.

Some of my colleagues believe that the report's emphasis on the carcinogenic potential of Zomax is misleading because reputable scientists can interpret the results of the Zomax animal carcinogenicity studies differently. The report, in their view, did not acknowledge the "debate" over the drug's cancer-causing potential. One of my colleagues questions whether FDA "properly reviewed" the rat studies and suggests that they might have been inconclusive. These criticisms overlook the central, and, I believe, proper purpose of the report. The report does not question the competence of FDA's reviewing scientists or attempt to determine whether Zomax is a potential human carcinogen. Rather, it examines FDA's regulatory performance in light of the *agency's own determination* that Zomax is a potential carcinogen. In determining whether FDA is properly enforcing the law, the report focuses on how FDA weighed the drug's benefits against a carcinogenic risk that had already been *identified by FDA's own scientists.*

As documented in the report, FDA believes, on the basis of animal studies, that Zomax has the potential to cause malignant tumors in man. Dr. Robert Temple, Acting Director, FDA's Office of New Drug Evaluation, testified during the subcommittee's hearings: "So we accepted the idea that the findings in rats could represent some degree of carcinogenic risk for man. That is true. I don't think anybody disagrees with it. That is why it is in the labeling. That is why there is a warning against chronic use." (See Hearings, page 159.) Referring to McNeil's proposal to "reposition" Zomax for long-term use, Dr. Temple recently wrote: "I said [at the subcommittee's hearings], and believe now, that such a repositioning alone would be unacceptable because of the animal tumorigenicity [capacity of Zomax to cause tumors]." (This statement is contained in an October 26, 1983, letter which is in the subcommittee's files.) Dr. Temple even characterized the low doses at which Zomax induced tumors in the rat as "scary." That Zomax has the potential to cause cancer in humans is clearly the conclusion of the Food and Drug Administration.

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Supporting Dr. Temple's testimony were the following findings and conclusions of FDA scientists, all of which were fully documented in the subcommittee's hearing record and cited in the report:

(1) The FDA pharmacologist responsible for evaluating the meaning and significance of the Zomax animal studies identified, in an October 25, 1979, review, a significant increase in adrenal medullary tumors among male rats fed Zomax in a two-year study.

(2) In a September 19, 1980, review, FDA's statistician characterized the evidence for the tumor-inducing potential of Zomax in the rat as "statistically significant." In other words, it is highly unlikely that the increased incidence of tumors among rats fed Zomax was a chance event unrelated to the administration of the drug.

(3) An FDA pathologist—the only agency expert who examined the rat tumor slides—diagnosed the tumors as "malignant".

(4) On May 20, 1980, FDA's pharmacologist *recommended nonapproval of Zomax* pending a determination of whether Zomax can be shown to have benefits which outweigh its carcinogenic potential. Noting that the potential carcinogenicity of Zomax was not seen with other approved NSAIDs, FDA's pharmacologist recommended at a minimum "a box warning in the labeling . . . alerting to the carcinogenic . . . potential based on 2 yr rat study." (Report, footnote 40.)

(5) At a November 23, 1981, meeting with FDA, McNeil was told that FDA scientists had concluded "that the incidence of rat lesions or tumors was significant enough to consider Zomax a tumorigen [tumor-inducer]." FDA officials at the meeting informed the company that no scientific evidence had been provided to permit the conclusion that the cancer-causing properties of Zomax in the rat had no relevance to humans. (Hearings, page 158.)

The dissenting views of some of my colleagues note that, in defending the approval of Zomax, despite the adverse findings and conclusions of its scientists, FDA did not consider the rat findings "ominous". However, not one pre-approval document written by an FDA reviewer attempts to minimize the significance of those findings. In fact, some of the features which FDA testified rendered the rat studies inconclusive (See Hearings, page 87) are actually contradicted by the documented conclusions of FDA's own scientists. (See, for example, Report, footnote 35.)

By questioning the evidence on the potential carcinogenicity of Zomax, it is, in fact, some of my dissenting colleagues who challenge the scientific findings and conclusions of FDA's experts. The report, by contrast, examines whether FDA, prior to approving a new drug which its experts have concluded is potentially carcinogenic, has weighed its benefits against its possible risks.

The dissenting views of some of my colleagues state that FDA does not approve new drugs unless their benefits outweigh their risks. Based on FDA's own scientific conclusions, however, the report documents that FDA approved Zomax without evidence that its benefits outweighed its carcinogenic risk.

The requirement that a drug with cancer-causing potential not be approved unless it is shown to be superior to marketed alternatives without such a potential is an established FDA policy. The

report's conclusion that FDA approved Zomax without meeting this standard is also based on the findings of agency experts. The committee is neither making its own scientific judgment nor, as one of my colleagues suggests, expressing subjective disagreement with FDA. As noted in the report, in approving Zomax FDA did not conclude that Zomax had been demonstrated superior to other NSAIDs that do not have a known carcinogenic risk. FDA testified in the hearings that, unlike other drugs in its class, some observers considered Zomax as equivalent to modest doses of morphine. However, FDA, not the committee, concluded that Zomax's equivalence to modest doses of morphine had not been established by adequate and well-controlled studies. Consequently, the agency never approved statements of such equivalence in the Zomax package insert.

Some of my dissenting colleagues state that FDA did not consider the rat tumors "ominous, *at least in short-term use*." (emphasis supplied) Although Zomax has been used primarily for short-term pain, its use to treat chronic pain was never contraindicated in the labeling. In fact, FDA expected Zomax to be used chronically and large numbers of Zomax patients were chronic users. Yet, it was FDA's conclusion that Zomax has not been shown to offer advantages over other NSAIDs for the treatment of chronic pain. In short, the report merely relies on FDA's own assessment of the scientific evidence offered in support of the relative benefits of Zomax.

It is an established policy of Federal regulatory agencies, as well as of Federal health research agencies such as the National Institutes of Health, that substances which induce tumors in animals can cause cancer in humans. The Committee on Government Operations has consistently recommended in past reports that FDA protect the public from drugs such as Depo Provera and DES that have been shown to be carcinogens in appropriate animal studies. At a time when we are spending vast amounts of public funds in a national effort to detect and control cancer-causing agents, I believe it imperative that FDA establish procedures which minimize the public's unnecessary exposure to such agents.

Section V of the report presented statistical analyses and other documentation showing that FDA disregarded important evidence relating to the dangers of serious hypersensitivity reactions to Zomax. Although some of my dissenting colleagues believe this section of the report "is not compelling," they have provided no analysis of its detailed findings.

Finally, some dissenters object that the finding that FDA improperly referred the Zomax remarketing question to its Arthritis Advisory Committee was not discussed during subcommittee hearings. It was during the subcommittee's hearings, however, that FDA presented the conditions which must be met before Zomax may be remarketed. FDA's subsequent failure to adhere to these conditions when it asked the advisory committee whether Zomax should be remarketed is integrally related to the hearings.

Moreover, even if references to the Arthritis Advisory Committee meeting were not directly drawn from hearing testimony, they are nonetheless a necessary and proper part of the report. The report is an "investigative report" as that term is used in the Rules of the Commit-

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tee on Government Operations. The hearings comprised only a part of the subcommittee's "investigation" of FDA's regulation of Zomax. I believe it wholly appropriate that the report should cover aspects of our investigation which were not specifically discussed during the submittee's hearings.

It should be noted that none of my dissenting colleagues challenges the substance of the report's finding that, in its regulation of Zomax, FDA made improper use of its Arthritis Advisory Committee. I believe all members of Congress—regardless of party affiliation—should be greatly concerned when agency officials take actions which impeach their testimony before a Congressional subcommittee.

TED WEISS.

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Exhibit E

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Finally, a New Chief for the FDA

His Job, Kessler Says, Is to Restore the Agency's Credibility

By Larry Thompson
Washington Post Staff Writer

Although the public swearing-in ceremony won't occur until later this month, a 39-year-old physician and lawyer from New York has taken over the Food and Drug Administration, an agency that has been without a leader for nearly a year.

David Aaron Kessler, the medical director of a 431-bed teaching hospital in the Bronx, comes to the FDA at a time when its credibility with Congress and consumers has been badly shaken by scandal in its generic drug divison.

Kessler will have to juggle several major problems at once—but then juggling has been his style. While training to be a pediatrician at the Johns Hopkins School of Medicine in Baltimore, he volunteered for night duty in the hospital so that he could spend the day in Washington as a staffer on the Senate's Labor and Human Resources Committee. His job was to draft food and health legislation. Colleagues remember Kessler in the emergency room, with the sirens screaming in the background, while he was on the phone reviewing the details of a bill. "That was typical," said Peter Barton Hutt, a former FDA general counsel who worked with him drafting legislation.

He also pursued a law degree at the same time that he was in medical school. For two years, he attended Harvard Medical School and then spent two years in law school at the University of Chicago. For his third year, he simultaneously attended law and medical schools at Harvard.

"I got both degrees in medicine and the law to run a hospital," said Kessler, the son of a jewelry manufacturer and a school psychologist. He also took a management training course at the New York University Graduate School of Business Administration. "I'm very good on organizational things," he said.

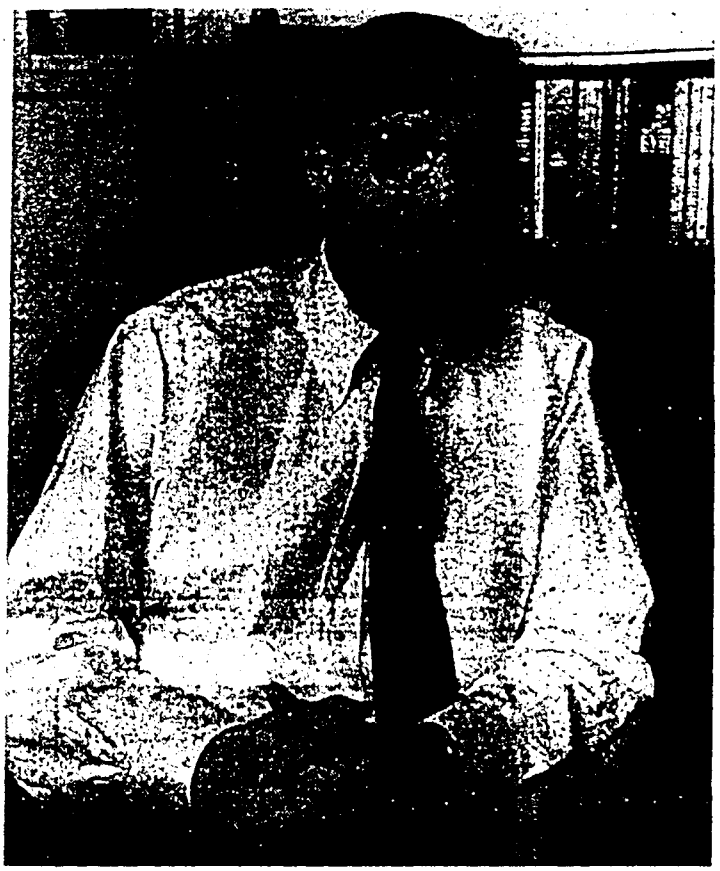
In 1984, Kessler became chief medical officer at the Jack D. Weiler Hospital in the Bronx, a part of the Albert Einstein College of Medicine-Montefiore Medical Center complex. At Weiler, he managed both patients and the medical staff, setting up a new cancer center, kidney program and special evaluation clinics for pediatrics and medicine.

Along the way, he married Paulette Steinberg, a lawyer. They have two children, Elise, 8, and Benjamin, 5.

Until his appointment to head the FDA, Kessler served on a commission set up by Health and Human Services Secretary Louis W. Sullivan to review the operations of the beleaguered agency.

The FDA regulates a vast array of products valued at $550 billion annually, goods ranging from cosmetics to canned vegetables to life-saving drugs. It oversees the nation's blood supply, monitors over-the-counter painkillers, tests both pocket-size pacemakers and $2-million-dollar imaging scanners.

The commission's report, due in May, is likely to call for more resources for the FDA, although no major new funds are expected in an era of tight federal budgets. "Kessler faces an enormous undertaking," said Charles Edwards, president of the Scripps Clinic and Research Foundation in La Jolla, Calif., and former FDA commissioner who heads the HHS panel.



JOHN TROHA FOR THE FDA

David Kessler will take over as Food and Drug Administration commissioner this month.

Among Kessler's most pressing tasks:

■ **Restoring public confidence.** The agency's credibility was damaged last year when four FDA officials were caught accepting bribes to speed up the approval of certain generic drugs, which are less costly versions of brand-name medicines. Several of the largest companies were caught sending the agency fraudulent information about their drugs. Ultimately, it is widely believed, the scandal cost former commissioner Frank E. Young his job last December, and, said several experts, has raised doubts in the minds of physicians and patients alike about the effectiveness of many drugs, both generics and brand names.

During the past decade, the FDA's enforcement actions have fallen sharply, in part, the agency's critics say, because of the philosophy of deregulation that characterized the Reagan administration. Inspections of products and food and drug manufacturing plants decreased from 36,258 in 1980 to 18,592 in 1989. Seizures of contaminated foods or adulterated pharmaceuticals dropped from 539 in 1980 to 142 in 1989.

Kessler says one of his first priorities is restoring credibility to the generic drug division. "We have to be sure that the agency is clean and that everyone who deals with it is clean," said Kessler. "I will need a little time."

■ **Building bridges to Congress.** Kessler has gotten off to a good start with congressional leaders, and his nomination sailed through in eight days. But it isn't clear how long the honeymoon will last. Sen. Edward M. Kennedy (D-Mass.), now chairman of the Labor and Human Resources Committee, for which Kessler worked, plans hearings on the FDA as soon as Congress reconvenes.

"It's going to be different for him," said Jere E. Goyan, pharmacy school dean at the University of California at San Francisco who served as FDA commissioner from 1979 to 1981. "In the past, he has been the good guy. That will disappear rapidly when things go wrong and he has to go down there as commissioner to explain why."

For two years, he attended Harvard Medical School and then spent two years in law school at the University of Chicago. For his third year, he simultaneously attended law and medical schools at Harvard.

"The question is how much independence he will have from the White House, OMB [Office of Management and Budget] and HHS," said Sidney M. Wolfe, director of Public Citizen Health Research Group, a consumer advocacy group founded by Ralph Nader. "I think he would like to get FDA back on track and do the right thing, but the leash is too short between the FDA commissioner and HHS."

■ **Speeding up approval of drugs.** The only serious questions raised during the Senate confirmation process came from AIDS activists who expressed concern that Kessler might not favor quick release of experimental AIDS treatments. Kessler says he supports this. "I'm a Bronx pediatrician," Kessler said. "I know what it is like to take care of dying children, especially those for whom there was no good treatment." Kessler told both Congress and AIDS activists that "patients with life-threatening diseases should have new drugs available to them at the earliest point at which there is reason to believe that the drug may be effective."

■ **Increasing resources.** Sagging morale and a crumbling infrastructure may be Kessler's biggest obstacle. What is likely to determine his success is how well he can lobby for more resources—positions and money—for his overwhelmed agency.

"If you add up all the new responsibilities placed by Congress on the agency, the resources have not kept up, and everyone recognizes that," Kessler said. Montefiore's $690 million annual budget for its medical school and hospitals, for example, is about the same size as the FDA's.

The FDA bureaucracy of 7,750 employees is scattered among 23 buildings in seven locations in the Washington area alone. FDA is not yet fully computerized: each new drug approval request involves so much paper that it fills a wall of shelves, often exceeding 200 volumes for a single application.

Kessler knows that he is taking on a daunting job and that change is likely to come slowly. "I'm no magician," he said. "But when people see that you can get things done, they line up behind you." ■

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182ND STORY of Level 2 printed in FULL format.

The Associated Press

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February 27, 1991, Wednesday, AM cycle

SECTION: Business News

LENGTH: 526 words

HEADLINE: FDA Pledges to Tighten Enforcement Regulations

BYLINE: By DEBORAH MESCE, Associated Press Writer

DATELINE: WASHINGTON

KEYWORD: FDA-Kessler

BODY:

The Food and Drug Administration, its reputation tarnished by the generic drug scandal, is trying to restore its credibility by strengthening enforcement across the range of its authority, the agency's new chief said Wednesday.

"There has to be a sense out there that there is a will to carry out the statute," which gives the FDA esponsibility for about one-quarter of all consumer purchases in the United States, Dr. David Kessler told reporters. "We are going to take enforcement up a notch."

To do that, he said, the agency is broadening its auditing of generic drug companies to include other industries with products that require FDA approval before they can be marketed, such as other prescription drugs, animal drugs and medical devices.

In addition, Kessler is creating a team of 50 criminal investigators this year and wants to double that next year to pursue cases of suspected fraud and other such misdeeds.

He is also considering increasing civil monetary penalties and procedures by which companies that deceive the agency through fraud or other serious crimes could be barred from further product approvals.

"Ensuring the accuracy of data presented to this agency is a high priority," said Kessler, who was sworn in Monday to head the agency, which regulates drugs, foods, medical devices and cosmetics.

Acknowledging that the FDA's budget of about $$690 million for this fiscal year is not enough to do all he wants, he said he is shifting resources to cover the highest priorities, including the stepped-up audits.

After uncovering fraud, bribery and corruption in the generic drug industry and the FDA's generic drug division, the agency changed the drug-approval process for these products.

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"The honor system is out the window," Kessler said. FDA inspectors now audit the information in companies' drug-approval applications to verify that the data is correct.

Previously, the agency relied on companies to be truthful. But the scandal uncovered numerous instances in which companies cheated on safety and effectiveness tests required for FDA approval. Dozens of drugs were taken off the market as a result.

Since July 1988,ve former FDA employees, five generic drug company executives, one consultant and three generic drug companies have been convicted on criminal charges.

The scandal reverberated through the industry and some observers say it had much to do with the resignation of Frank Young as head of the agency in the fall of 1989.

Kessler said that while expanding the pre-approval inspection audits to other prescription drugs, he will be mindful of not lengthening the time it takes for products to be approved, which has been a persistent criticism of the agency.

"The goal is to assure quality of what's out there without lengthening review time," he said.

So far, FDA inspectors have found "discrepancies" in some of its audits, Kessler said, but no cases of outright fraud. The problems, he said, involve such matters as sterilization and potency.

Kessler, a 39-year-old pediatrician and lawyer, left a job teaching food and drug law at Columbia University School of Law in New York to head the FDA.

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New Chief Vows New Vitality at F.D.A.

By PHILIP J. HILTS
Special to The New York Times

WASHINGTON, Feb. 26 — Saying he intended to revitalize an overburdened agency, the new Commissioner of the Food and Drug Administration said today that he would get tough in enforcing its regulations while seeking to approve new drugs more quickly.

As a first step, the new Commissioner, Dr. David Kessler, said he would create a team of 100 criminal investigators over the next two years to pursue cases of fraud and other serious violations of the food and drug law.

He was sworn in Monday to head an agency that many experts in Congress, industry and consumer groups say has been in crisis for several years as the agency's staff has shrunk while its duties have expanded.

Dr. Kessler's appointment comes at a crucial time for the agency. On the issue of new drugs, its emphasis is changing from holding them off the market in order to assure safety to responding to demands, many from AIDS patients, that new drugs be released sooner. But its credibility has been challenged in scandals ranging from favoritism in the approval of generic drugs to lapses in regulating health claims on foods.

Trouble With Deadlines

The agency has been so burdened with new responsibilities and so short of staff to deal with them that it almost routinely fails to meet its own deadlines for issuing regulations. In the last decade, the AIDS epidemic has dramatically increased the demands on the agency, even as Congress has passed laws giving it new responsibilities for inspecting drugs, medical devices and foods. And budget cuts have left it with a smaller staff than it had as the 1980's began.

But many experts think Dr. Kessler has the best credentials of any commissioner in many years to save the agency from breakdown.

"If you had to write a fictional résumé for the perfect person to hold this job, it would turn out to be David Kessler's résumé," said Peter B. Hutt, a lawyer who is a consultant to the agency and serves on some of its panels. "If he can't do it, no one can."

In taking over the new job, Dr. Kessler said that two of his chief priorities would be to beef up the agency's power of enforcement, and as the same time streamline the many-layered procedures that can delay approval for drugs and medical devices by months or years in some cases.

Subpoena Power Sought

He said he would ask Congress for new powers for the agency, including subpoena power for his 100 new investigators and the authority to levy civil penalties against companies if they violate the law but the offense is not serious enough to warrant criminal action. In addition, he said, he will seek the power to allow the agency's inspectors — who monitor everything from the manufacture of drugs to pesticides on tomatoes arriving at the border — to inspect records.

Representative Henry A. Waxman, Democrat of California, the chairman of the House Subcommittee on Health and the Environment, said today: "I applaud Dr. Kessler's commitment to law enforcement, which is essential to the F.D.A.'s effectiveness as an agency. I am anxious to work with the agency to provide it with the new enforcement tools it needs to do it's job."

Senator Edward M. Kennedy, Democrat of Massachusetts, the chairman of the Senate Labor and Human Resources Committee, which has jurisdiction over the F.D.A., gave Dr. Kessler encouragement today when he said through a spokeswoman: "The Food and Drug Adminstration is caught in a downward spiral of declining resources, credibility and morale. Dr. Kessler has the background to deal effectively with the latter two problems. If he does, he'll find Congress ready to provide more resources."

Dr. Sidney Wolfe, head of the Public Citizen Health Research Group, an advocacy groups specializing in health matters, said that Dr. Kessler's appointment is very promising. "He comes at a key time, after the worst leadership in F.D.A. history, which demoralized the agency unlike anything I have ever seen," Dr. Wolfe said. "In the past, we had to sue them to put warning labels on tampons to prevent toxic shock and sue them to ban unpasteurized milk."

> A 100-member force to pursue food and drug violations.

Scrutiny on Drug Industry

One example of Dr. Kessler's promising action cited by Dr. Wolfe was that the new Commissioner has doubled the size of the staff working on advertising and promotional abuses by the drug industry.

Althouth the agency's budget has increased in the past two years, it was not immediately clear where the money to pay the new investigators would come from. "Where will they get the money for the investigators?" asked one staff member of the House Subcommittee on Oversight and Investigations.

The subcommmittee is headed by Representative John D. Dingell, a Michigan Democrat who has been a persistent critic of the agency and who has conducted several inquiries into its operation.

Further, the aide said, the agencies recent troubles might make it difficult to recruit. "It will be hard for them to recruit experienced people," the staff member said.

But in general, Dr. Kessler's reception has been so good, and the relief expressed so widespread that Mr. Hutt said one danger might be expectations that rise too high too fast. "This agency is still in trouble in many ways," he said.

Resigned Under Pressure

The former permanent Commissioner, Dr. Frank E. Young, resigned under pressure in the fall of 1989 after several agency and industry officials were convicted in connection with a scandal in which companies faked safety and effectiveness data for generic drugs that went on the market.

The new Commissioner is 39 years old and is both a lawyer and doctor. He graduated from the University of Chicago Law School in 1978 and the Harvard Medical School in 1979. Dr. Kessler also worked on F.D.A. issues, for Senator Orrin G. Hatch, Republican of Utah, and taught food and drug law at the Columbia Law School in New York from 1986 until he was named Commissioner in December 1990. A pediatrician, he was also the director of medicine at Albert Einstein College of Medicine in the Bronx from 1984 until he became Commissioner.

The Food and Drug Administration is often said to be the most influential regulatory agency on earth, with responsibility for the safety and effectiveness of one-quarter of the nation's gross national product, and an expertise that other nations routinely rely on.

But as Dr. Kessler said in the interview, to cover hundreds of billions of dollars of American and imported products, the drug agency has a budget about the same as the Albert Einstein medical school and the Montefiore Medical Center.

The school and medical center budget is about $690 million annually, and the F.D.A.'s budget is about $690 million for the fiscal year that began in October, he said.

Bigger Budget Is Vision

Dr. Kessler hopes to increase the agency's budget and was helped by a Bush Administration increase for 1991 and a proposed increase for 1992 that would raise financing by 43 percent in the two years if Congress agrees to the 1992 proposal.

In a speech at a recent meeting of the Food, Drug and Law Institute, a trade group, Dr. Kessler said his first priority was restoring the agency's credibility.

Of all of his tasks, he said, it was "the most difficult one to talk about." He went on to express his ideas about the agency this way:

"It is the most difficult one because I know that F.D.A. employees are deeply committed to their mission. But it must be said: 'The most important thing we can do to rebuild the credibility of the agency is to insure the integrity of its processes.'

"Some may argue that by stessing integrity, I express a lack of trust in the agency. I mean nothing of the sort. In fact, I think I know how F.D.A. employees feel: deeply angered that all should be tarnished by the gross misconduct of a few."

Michael Geissinger for the New York Times

Dr. David Kessler, new Commissioner of the Food and Drug Administration, plans to add 100 new criminal investigators.

John C. Petricciani, vice president for medical and regulatory affairs of the Pharmaceutical Manufacturers Association, which represents the large pharmaceutical companies, said the industry was encouraged by Dr. Kessler's appointment.

'A Gut Feeling'

"I have a gut feeling that Dr. Kessler's appointment has the potential for being one of the most important in the agency's history," he said. "It comes at a time when the agency is trying to decide what it's mission is — traditionally it has been, very heavily, to protect health, but now the availability of new drugs is becoming almost equally important."

Speeding the approval of new drugs, especially those for life-threatening illnesses like AIDS and cancer, is near the top of his list of priorities, Dr. Kessler has said.

But Mr. Petricciani suggested that the agency should not spend additional dollars on criminal investigators. "What is the mission of the agency?" he asked. "Is it law enforcement? Some would argue that it is not. It has some regulatory responsibility, but to the extent it gets into law enforcement, that is not the mission of the agency.

"There are a finite amount of resources, and the F.D.A. should put its money where Congress and the public perceive its mission to be," like drug approval, he said.

Company News:
Tuesday through Friday,
Business Day

A GREAT PLACE

The bank acc

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MICHAEL SCHRAGE

Consumers Deserve Honest, Direct Advertising of Prescription Drugs

For the average American, the most provocative breakthrough in medical care this decade might not come from researchers at the National Institutes of Health but from the copywriters on Madison Avenue.

While the health-care establishment may find prescription drug advertising aimed at consumers as appealing as a spinal tap, smart consumers should welcome it. Health-conscious people today crave knowledge and awareness about their options. Precisely because doctors still do a far better job prescribing medicine than information, consumer advertising must play a far larger role in stimulating dialogue between patients and physicians.

Currently, there's only a smattering of prescription drug ads—and they do more to tease than enlighten. Regulators concede that changes are needed.

Obviously, advertising doesn't qualify as informative when it features a jut-jawed Lee Iacocca-type executive blustering in the pages of Time magazine that "Whenever I feel my ulcer acting up, I reach for my Tagamet," or some come-hither blonde cooing on Lifetime cable that "I know that a man who can afford Rogaine is a man who can afford me." Pharmaceutical ads shouldn't promise ecstasy; they should encourage questions.

The real issue isn't whether advertising can hype prescription drugs the way it hypes Chevrolets or Miller Lite. It is where to draw the line between promoting effective awareness and encouraging foolish consumption. As a matter of public policy, isn't it a good idea to let people know what new medicines are available? Or is a tight-fisted regulatory paternalism necessary to eliminate even the shadow of possible consumer misunderstanding?

"The Food and Drug Administration is kind of grappling with its policy on direct-to-consumer advertising," acknowledges FDA Commissioner David Kessler, who hopes his agency will have a plan to regulate drug advertising and promotion by the end of this year. "It's very hard, in my opinion, to achieve fair balance. . . . For example, I'm not overly impressed with the information conveyed in any pharmaceutical drug advertisements."

Quite properly, Kessler's FDA has been cracking down on false or misleading advertising—punishing companies that contend that their products are "fresh" when they're not. But eliminating misrepresentation on labels is not the same as promoting awareness of medicines. If it is clever, the FDA can craft a policy that could lead to better-informed consumers and a more competitive pharmaceutical marketplace.

"The public is entitled to and should have maximum information about health-care products—including prescription drugs," says Wayne L. Pines, a former FDA associate commissioner who wrote an article last year with Kessler on consumer drug advertising. "What we need is a debate on this very subject," says Pines, an executive vice president at the Burson-Marsteller public relations firm.

That debate has been conspicuously lacking. Ever since 1981, when the then-FDA commissioner made a speech to an industry group predicting exponential growth of pharmaceutical ads, the issue has been shaped less by public interest than by political loopholes.

The FDA has alternately banned such ads, regulated them with rules originally targeted for physicians or given pharmaceutical companies wide latitude—so long as the ad doesn't mention the product's name. For example, ads mentioning the brand name must include all the relevant medical information, such as possible side effects (a rule intended to keep them off television).

That's one reason American Medical Association member surveys consistently show strong opposition to direct-to-consumer advertising. "Since 1984, we've done two major surveys, both indicating that roughly 85 percent of physicians are opposed to direct advertising," says Donald R. Bennett, director of the association's division of drugs and toxicology.

Nevertheless, Bennett points out that the trend is toward better-informed patients who are willing to challenge their doctors. Ads designed to promote doctor-patient dialogue instead of sales would probably meet with less resistance, Bennett contends.

For example, an ad that starts, "What you need to know about hypertension if you are a black male between the ages of 28 and 50" encourages the target group to seek out a doctor's advice—not a prescription for a drug.

"There is the misconception that these ads will undermine the expertise of the learned practitioner," says Elizabeth A. Moench, Ciba-Geigy's executive director of public affairs. "In fact, ads that encourage awareness will not."

"While I'm personally supportive of efforts to educate patients about drugs," FDA's Kessler says, "once one crosses the line into promotional aspects, I become skeptical about the benefits. . . . Once you're into the realm of promotion, it's very hard to control the messages."

Just because it's difficult doesn't mean that it can't be done. Instead of simply promulgating guidelines, the FDA should give serious thought to setting up a council of advertising, pharmaceutical, medical and regulatory representatives to create maybe five or six different "formats" for direct-to-consumer advertisements for print and video. These formats would be structured to encourage patient-physician dialogue and would include information relevant to general consumers.

Ads that fall outside these formats wouldn't be FDA-approved. Ads that conform would be reviewed by a standing council—but the FDA would have the right to veto the council's recommendation.

For the first few years, companies could be limited to maybe six consumer-ad submissions a year. If the council let through too many questionable ads, the FDA could slow the approval rate. If the ads fostered the appropriate balance of promotion and awareness, the approval rate could accelerate.

Ultimately, prescription drugs might play as big a role in the media as their over-the-counter brethren.

Is that bad? Or is it simply a necessary part of making people aware of the choices available to them? Whatever the FDA decides, the issue of advertiser-supported medical information is going to become more important over the next decade, not less.

Michael Schrage is a columnist for the Los Angeles Times.

Long-Term Interest Rates Stagnate

RATES, From F1

homeowners across the country it averages around 9.5 percent.

While the Federal Reserve has pumped enough money into the nation's banking system to reduce key short-term rates by 2.5 percentage points since the recession began, long-term rates have dropped only about one-third as much—and there seems to be little the central bank can do about it.

Allen Sinai, chief economist of the Boston Co., a Boston-based economic advisory firm, said the wide spread between short- and long-term rates is typical of the latter stages of a recession. "It reflects the cuts in short-term rates and the lag between the recession and the improvement in inflation" the recession usually generates, Sinai said. "We have had only two months of good inflation news, not enough . . . to change [investor] expectations about investors usually demand yields high enough to give them not only a "real" rate of return but an "inflation premium" as well to protect the value of the money they have invested. The inflation premium plus the real return add up to the interest rate investors require before making their money available.

"On this, the bond market is very backward looking," Sinai said. "Investors are not going to be persuaded that the inflation rate is lower before they have four, five or six months of news that it is actually lower."

If long-term rates do not come down, whether because inflation does not fall as many forecasters expect or for some other reason, "then we will have a weaker recovery" than the relatively modest one now predicted, Sinai said.

"If long-term rates do not come down by half to three-quarters of a point over the next six months the recession stuck at their present levels would fall on home building and all the industries supporting it, such as forest products, furniture, cement, real estate brokers and mortgage lenders. It also would be seen in business capital spending, where the level of rates affects not only actual borrowing but calculations about whether individual business projects offer large enough profit opportunities to make them worthwhile. If yields on alternative investments—including even buying back a portion of a company's common stock—are higher than the return on a new business project, the project will not see the light of day.

Many economists believe that inflation will be lower in coming months than the 4.9 percent increase in consumer prices seen over the past year. For instance, the National Association of Business Economists (NABE) yesterday said its quarterly survey of 58 forecasters showed they expect prices long-term interest rates is less clear. Sinai believes it will be. But despite lower inflation, the NABE group projected little change from current interest rate levels as the U.S. economy begins to recover from the recession.

Other analysts said that aside from expected inflation, there are two other major forces helping keep long-term rates high, the level of real rates of return in Europe and Japan and the huge amounts of money the U.S. Treasury is borrowing this year to finance record federal budget deficits.

Real rates are high in Germany because of the enormous financial strains of coping with the problems in what was formerly East Germany. They are high in Japan in part because the Bank of Japan is trying to squeeze the economy to contain inflation and halt the rise in real estate values.

Since all these financial markets are integrated to a degree, rates in one country affect those elsewhere. Thus, the costs of cleaning up the environmental mess in Germany may make a difference in the rate a home buyer in Fairfax County may have to pay to get

To Be Small is Beautiful In Mini-Cellular-Phone War

PHONES, From F1

The difference that Fujitsu is crowing about is not pounds or even ounces. It is tenths of ounces. In this case, the Pocket Commander is four-tenths of an ounce lighter than the MicroTAC. Models made by other manufacturers weigh in close to that.

"We're talking fractions of ounces here," said Herschel Shosteck, president of Herschel Shosteck Associates, telecommunications economists in Silver Spring. "I'm sure Fujitsu is correct, but from a technical point of view, one- or two-tenths of an ounce has no relevance."

Small, however, does not mean cheap: Microportables retail from $799 to $1,199. A mid-range phone, on the other hand, can go for $339.

But price has not been a deterrent to sales over the past few years.

Sales of portable cellular phones are if they come up with better battery technology, they will be lighter."

The Pocket Commander with a full-size battery weighs 12 ounces and provides 80 minutes of "talk time" before the battery needs to be recharged. The slim battery, which costs an extra $107, offers 45 minutes.

Motorola offers 100 minutes of conversation on its big battery and 30 minutes on its slim model.

The attraction for consumers is that these phones can go anywhere and are small enough to be slipped inside a pocket. The hope is that users who have made "big" cellular phones extensions of their offices will make "little" ones part of their personal lives.

Fujitsu, which manufacturers the Pocket Commander in Richardson, Tex., has rolled out a nationwide print and cable television advertising campaign claiming it has broken "the com-

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LOS ANGELES TIMES, MARCH 7, 1991, PG A4

husband Nelson, enters the ... trial on kidnaping charges.

a Whipped s Testifies

...ping victim takes stand ...es beating of slain boy

...ings occurred in a back room of ... Mandela's Soweto home. He ... she punched Seipei "for a ...siderable amount of time," dur... which Seipei denied being a ...ce informant, Kgase said Seipei ...eared to be "feeling pain."

Kgase said Mrs. Mandela went ... one man to another punching ... of them and then the others ... room joined in.

"There was pandemonium," ...ase said. "I got myself punched ... many people I was severely ...ched for a long time. I can't ...ember how it stopped."

During the beatings, Kgase said, Mrs. Mandela was humming a ... and dancing to the ...

"All of a sudden," Kgase added, "I saw her having a sjambok ...nip), and she started with me ... . . . Before she said any-...ing she struck several blows."

He said he fell to the ground and ...ied to shield himself as others in ...e room were sitting and watch-...g. When she stopped hitting ...m, Kgase said, she returned to Seipei.

Then, Kgase said, three of the ...en in the room picked up Seipei ...nd dropped him twice on his head. Others in the room beat Seipei ...verely with sjamboks until his face was bloody and his head swollen, Kgase said. As the beat-...ngs continued, Mrs. Mandela left the room, he testified.

Seipei's body was found a week later in a Soweto field.

Dr. Patricia Klepp, who performed the autopsy on Seipei, testified that he had been stabbed three times in the neck and beaten severely on the head and body. She said either the stab wounds or the head injuries could have caused his death.

Under questioning, Kgase said he knew of no homosexual incidents at the church house, which is run by the Rev. Paul Verryn, a widely respected pastor in Soweto.

Verryn still runs the church house, and Mrs. Mandela has sent dozens of young men to his halfway house for shelter in recent months. An internal investigation by the Methodist Church found no evidence of sexual misconduct by Verryn.

Kgase testified that on Dec. 31, 1988, two days after the beatings, Jerry Richardson, the leader of Mandela's bodyguard, came to the house with another man, whom Kgase could not identify. Richardson said Kgase, Mono and Mekgwe had been pardoned but that Seipei had admitted selling out four "comrades," who were shot to death by police officers.

Richardson was convicted last year and sentenced to death for Seipei's murder.

Kgase escaped from the Mandela home on Jan. 7, 1989, and, two weeks later, after pressure from community leaders, Mono and Mekgwe were released.

Dr. Martin Connell testified ...

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says. Prime minister calls demands unreasonable

By ELIZABETH SHOGREN
TIMES STAFF WRITER

MOSCOW—A spreading Soviet coal miners strike that stretches from the Ukraine to western Siberia will continue until Soviet President Mikhail S. Gorbachev resigns, a leader of one of the largest strike committees said Wednesday.

"Under Gorbachev's leadership, we're living our lives by ration coupons," said Yuri V. Komarev, co-chairman of the strike committee in the western Siberian city of Novokuznetsk, the center of the country's second largest coal area. "We will stay on strike until Gorbachev and his team resign."

The strike began late last week in the Ukraine and the Central Asian republic of Kazakhstan and on Monday spread to mines in western Siberia.

In the Ukraine the mines on strike have increased to 21, according to Andrei O. Slivka, a member of the strike committee in Donetsk, the heart of the largest Soviet coal field. At 11 more mines in the Donetsk Basin, miners are still at work but they are refusing to ship the coal, he added.

In western Siberian coal fields, four mines are on strike, idling 70,000 workers, and five others are refusing to ship their coal. Workers at 28 mines, more than a third of those in the coal-rich region, held a 24-hour warning strike, according to Komarev.

Slivka said many more mines would like to participate in the strike but that management at those enterprises has threatened to fine strikers 200 rubles a day, or half an average month's pay. Local officials have warned that "agitators" will be prosecuted and jailed.

But many miners apparently would not be deterred.

"No fewer than 100,000 miners are striking right now," Slivka said in a telephone interview. "This strike should show Gorbachev that, when his government makes pledges, he should be responsible for them."

... back on the job in the summer of 1989, when more than 500,000 miners across the country struck for two weeks.

Although the current strikes do not approach the 1989 crisis in scale, they are weakening not only the Soviet energy industry but other sectors of the economy, including steel production, that depend on it, and the Kremlin is clearly worried about the overall impact.

Prime Minister Valentin S. Pavlov, speaking on Soviet television Tuesday, appealed to miners to return to work and called their demands unreasonable at a time when industrial production across the country is plummeting.

"I would like to raise everyone's pay tomorrow as high as the miners wish," Pavlov said during an interview on "Vremya," the evening news program. "There's only one question: Where will we get the money?"

Pavlov said the country's production has dropped 5% since the beginning of the year and that the miners' productivity has declined over the last three years.

"I want the miners to understand that they have no enemies in the government," the prime minister continued. "But we have to look objectively and realistically at what we can do and when we can do it."

The demands of the strike vary from mine to mine. Although some mines had only economic demands, the Bolshevik Mine in Novokuznetsk demanded that a question of no confidence in Gorbachev be added to the countrywide March 17 referendum on preserving the Soviet Union as a federal state.

Many miners said they support Russian Federation President Boris N. Yeltsin, who has emerged as Gorbachev's chief rival. "We support Yeltsin . . . not because of his nice name but because of his concrete deeds and his policies," Komarev said.

The strike has also reached into southern Russia, where 18 of the 101 mines in the Rostov-on-the-Don region were on strike, the labor newspaper Trud said.

... spectacular. But he said the trees' delicate blooms are vulnerable to cold weather, high winds and driving rain.

An early flowering, however, can create problems for the annual Cherry Blossom Festival, scheduled for March 31 to April 7.

Parks service chief scientist William Anderson has examined indicator trees—those that consistently bloom early each year—and predicted they will be in blossom within a week, Kittleman said. The rest of the trees would follow in a few days.

The 3,000 trees that line the Potomac River near the Jefferson Memorial were a gift from the government of Japan during the administration of William Howard Taft. His wife and the wife of the mayor of Tokyo planted the first cherry tree in 1912.

New Commissioner Vows to Restore Integrity to FDA

By MARLENE CIMONS
TIMES STAFF WRITER

WASHINGTON—The new commissioner of the Food and Drug Administration told members of Congress on Wednesday that his first priority will be to restore the integrity of his beleaguered agency.

"The FDA is on the move," said Dr. David A. Kessler, outlining his agenda during his first public appearance on Capitol Hill. "We have vigorously begun our work. . . . We are building the momentum that will sustain us in the months and years ahead."

Kessler, a pediatrician and an attorney, said he intends to protect against future abuses by revamping the ways in which the FDA reviews the data upon which it bases its approval of various products.

"The lesson the last several years have taught us is that it is imperative that we audit the data . . . ," he told the Senate Labor and Human Resources Committee. "We have found fraud and misleading data, and it is possible that these practices are more widespread than we thought likely."

Kessler said he also plans to strengthen the FDA's enforcement and surveillance programs to safeguard against the type of scandal that shook its generic drugs division last year. A federal investigation found that several FDA regulators had taken bribes from officials of generic drug companies in exchange for hastening the approval of their products. Five FDA employees have been found guilty, and four firms and eight drug company executives have pleaded guilty to making the payoffs. Others are still under investigation.

"I believe the generic drug situation occurred because people . . . thought they could get away with it," Kessler said. "We are enhancing our efforts in this area by hiring additional criminal investigators, providing more training for all investigators, streamlining our enforcement procedures, and having FDA headquarters pay more attention to field activities," he added.

The new FDA chief was sworn in last week and was confirmed by the Senate before it adjourned last year, but he did not have a confirmation hearing. At the time, he promised to appear before lawmakers to discuss his objectives for the agency.

Before coming to the FDA, Kessler was director of medicine at Albert Einstein College of Medicine in the Bronx.

In outlining his objectives Wednesday, Kessler said he also hopes to bolster the agency's surveillance activities in such areas as medical devices; inspections of imported products, which have tripled since 1970 and which "tend to have more violations;" and in food products where there can be problems with disease-causing organisms, such as salmonella.

He added that he wants to find ways to manage the growing volume of applications for such items as new drugs, food additives, and blood bank licensing. Currently, he said, the agency "is not adequately prepared to meet the anticipated demand of new applications."

He said he was also concerned about violations of FDA regulations that govern prescription drug advertising, saying "it is clear to me that some in the prescription drug industry have gone over the line." Consumers are being "misled" by some promotions, he said, and "unless we act swiftly . . . they will almost certainly result in the kind of chaos that we saw recently with health claims on the food label."

Kessler acknowledged that his program was ambitious, saying: "We have a lot to do here. It will take my entire tenure, and it will go beyond one commissioner."

India's Prime Minister Quits After 3 Months; New Elections Probable

From Associated Press

NEW DELHI—Prime Minister Chandra Shekhar resigned in anger Wednesday, accusing former Prime Minister Rajiv Gandhi and his political party of betrayal and making new elections a virtual certainty.

Shekhar, a veteran politician but a novice in the top circles of government, served three months as head of a minority government in India, the world's largest democracy.

Gandhi, 46, who helped to get Shekhar elected as prime minister, also helped to end his term by withholding support needed to pass bills in Parliament.

Six hours after the prime minister announced his resignation, Gandhi's Congress Party declared that it wanted new elections, echoing the urgings of Shekhar and leaders of the major opposition parties.

It is up to President Ramaswami Venkataraman to decide whether to call new elections or to ask someone else to form a government. But the president, whose post is largely ceremonial, appeared to have no choice since the six largest parties in Parliament say they do not want to try to form another coalition government.

In the meantime, Shekhar said he will continue to serve as prime minister "until new arrangements are made."

New elections might again fail to determine a clear winner and leave the country with another fragile minority government like the one headed by Shekhar or that of his predecessor, Vishwanath Pratap Singh. Singh served 11 months after dislodging Gandhi in the November, 1989, elections.

Shekhar announced his resignation on the floor of Parliament with biting remarks. He had just listened to two hours of tirades by opposition members who accused him of running a puppet government whose strings were pulled by Gandhi and Gandhi's Congress Party.

"I cannot run the government in keeping with their [the Congress Party's] behavior," Shekhar said.

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New Chief Makes FDA a Regulatory Tiger

■ Government: He is intent on restoring public confidence in the agency. Businesses are getting the word that deception won't be tolerated.

By MARLENE CIMONS
TIMES STAFF WRITER

WASHINGTON—After years of restraint—some would even say timidity—the federal Food and Drug Administration in recent weeks has become the regulatory tiger of the Bush Administration, aggressively attacking the food industry for deceptive claims on a variety of products.

With a series of sharply worded warnings, court actions and even one warehouse seizure, the agency has jolted food companies long accustomed to deferential treatment by the government. The change has surprised even some FDA officials, who for years had been discouraged from taking action except in cases of life or death.

Most of the impetus for the agency's sudden personality change comes from its new commissioner, Dr. David A. Kessler, a physician and lawyer and an unlikely activist in an Administration that still officially adheres to the theme of getting government off the backs of business.

"He has sent a very powerful message," said Jeffrey Nedelman, a spokesman for the Grocery Manufacturers Assn. "He has our attention."

The agency regulates a broad array of consumers products, including foods, drugs, cosmetics and medical devices.

In recent weeks, the FDA has aimed its enforcement guns at several major food companies, forcing them, for example, to remove the word *fresh* from their product labels because the foods, in fact, are processed.

And, this week, the agency moved against manufacturers of several vegetable oils and other items for using the words *no cholesterol*, charging that the designation was misleading because cholesterol is a substance found only in animal products.

"We recommended several times that we take at least some kind of symbolic action, just to show we weren't tolerating this kind of thing—and we were turned down from above time and time again," said Sanford Miller, who was director of the FDA's Center for Food Safety and Applied Nutrition from 1978 to 1987.

"He's going against the big guys in the forest—that's what we wanted to do, take on a big food company or a big drug company and say, 'This is the law and you're compelled to follow the law just like anyone else,'" said Miller, now dean of the graduate school of biomedical sciences at the University of Texas Health Science Center in San Antonio.

"But the philosophy of the [Ronald] Reagan Administration was: the less regulation, the better. They never came to grips with the idea that someone had to make sure that everybody was following the rules, that everyone was playing on a level playing field.

"The interesting thing is that the bulk of the industry suffers when the FDA doesn't enforce the law. Time and time again, companies would come to us and say, 'do something'" about the other companies.

Kessler said that he was not seeking to proliferate regulation or to put his bureaucracy in everyone's business but that he was insistent on enforcing the laws and restoring public confidence in his beleaguered agency.

For years, "people thought they could get away with things," he said in an interview. Now, he said, that will change—and the impact could be broad, because industries that fall under the FDA's authority touch the daily lives of all Americans.

"The issues go well beyond *fresh* and *no cholesterol*," Kessler said. "They go to the willingness of the agency to enforce the statutes. If American consumers can't believe their government is going to protect them from dishonest and unfair dealings, they won't believe their government will protect them against unsafe substances either.

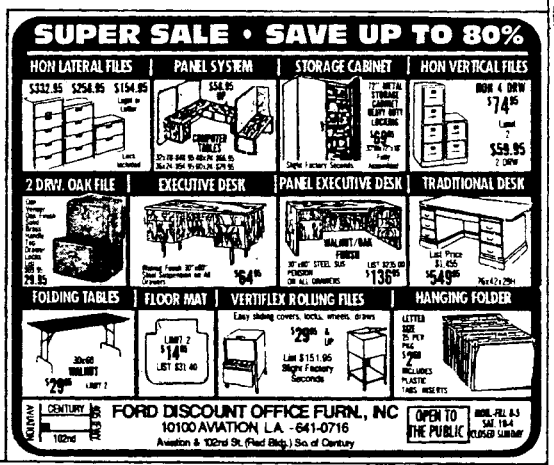
"If you let false and misleading actions happen, that translates into people thinking they can get away with things," he said. "And one day you will end up with unsafe and dangerous things happening."

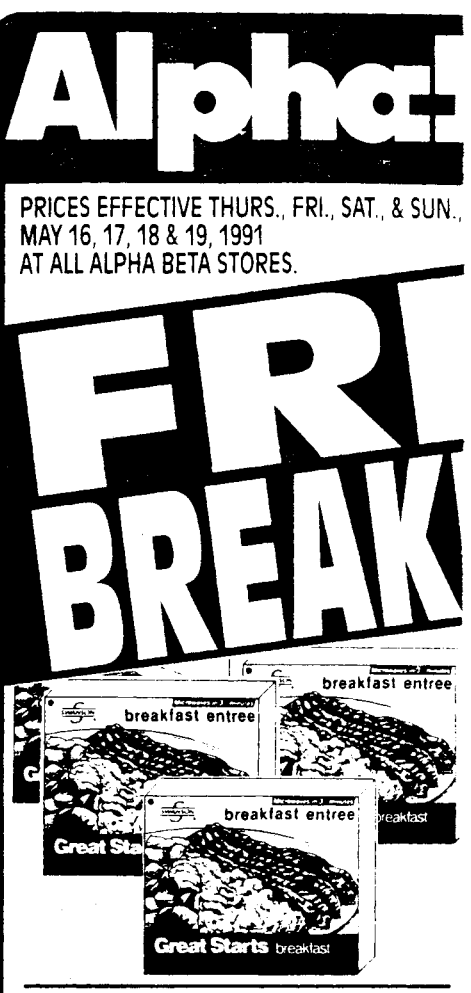
In recent years, the agency has been laboring under the handicaps of limited resources, a shrinking staff and serious erosion of public respect.

"Enforcement is only a tool," Kessler said. "It's not an end in and of itself. It's the incentive to assure compliance. In the past, the industry would say, 'Let's fix only what we've got to fix.' The incentive to comply wasn't out there."

But now it is, industry executives acknowledged Wednesday. "I can assure you that industry has gotten the message," said Peter Barton Hutt, a Washington food and drug lawyer whose clients include many large food companies. He predicted that companies will now begin to police themselves. "Any intelligent lawyer would advise his clients to do so," he said.

He contended that industry welcomes the changes because the system will now be made fair for everyone.





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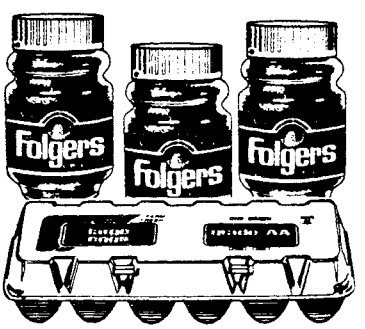

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The Watchdog Wakes Up

Food companies can forget the days of anything-goes regulators. A new FDA commissioner is cracking down on deceptive labels.

By ANASTASIA TOUFEXIS

For a while now, the makers of many vegetable oils have had a nice little gimmick going. On their bottles, in big, easy-to-read letters, are the words "no cholesterol," sometimes printed with a cute drawing of a healthy heart. The implicit message: Cook all the French fries you want in this oil and don't worry about heart disease.

The only problem with this marketing ploy is that it is nonsense. Cholesterol is found only in foods from animals, and thus putting "no cholesterol" on a vegetable-oil label is misleading. More pertinent to the consumer is the fact that the oils are a liquid form of fat—pure fat. And high-fat diets have been linked to heart disease, breast cancer and a variety of other ailments. So hold the French fries.

Not so long ago, the food industry could pull this kind of shenanigan with impunity. But that was before the emergence of the new Food and Drug Administration. Not the old, demoralized, anything-goes agency whose officials accepted bribes for approving untested generic drugs, but an FDA that seems to be rededicated to protecting the public. Last week the FDA ordered Procter & Gamble, the manufacturer of Crisco Corn Oil, along with Best Foods, which markets Mazola Corn Oil, and Great Foods of America, maker of HeartBeat Canola Oil, to cut out the "no cholesterol" business. While Best Foods and Great Foods stalled by saying they would work with the FDA to resolve the dispute, P&G went ahead and announced it would drop the offending words from Crisco—and also voluntarily remove the "no cholesterol" claim from Duncan Hines cake mixes, Fisher Nuts, Puritan Oil and Pringle's potato chips.

It was the second time in three weeks that the FDA had dared challenge the big food companies. The first target was Citrus Hill Fresh Choice orange juice, another P&G product. After more than a year of wrangling over the word "fresh" (the product is made from concentrate and is pasteurized), the FDA had U.S. marshals impound 24,000 half-gallon cartons of the juice at a suburban Minneapolis warehouse. P&G gave in within two days. Unilever subsidiary Ragu Foods, which since 1989 had been skirmishing over the same word on labels for its processed pasta sauce, soon dropped its fight. And earlier this month two other companies revealed that they were removing "fresh" from pasta sauces: Nestlé from the Contadina brand and Kraft from DiGiorno sauce.

The architect of the new FDA is David Kessler, 39, who became commissioner last December. Kessler is a far cry from the Rita Lavelle–style, wine-and-dine-with-the-industry regulators who reigned during the Reagan years. With a degree in medicine from Harvard and one in law from the University of Chicago, he understands health issues and knows how to devise and enforce tough regulations. In the early '80s he served as a consultant on FDA matters to Utah Republican Senator Orrin Hatch, who brought Kessler's talents to the attention of the Bush Administration. But the White House, with its friends in Big Business and its fealty to the philosophy of deregulation, may not have expected so much activism so soon. "I have no problems making decisions," declares Kessler, who is investigating several strategies to bolster FDA enforcement. Among them: levying fines, giving subpoena powers to agency inspectors and searching through corporate records.

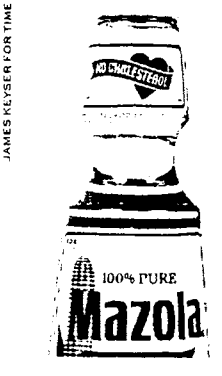
Food companies contend that the confusion about their labeling stems not from deception on their part but from the government's failure to issue clear guidelines for making nutritional and health claims. The FDA plans to set forth revised labeling rules next year. "Once these regulations are out," says John Cady, president of the National Food Processors Association, "industry will know clearly what the FDA expects and will certainly comply." Cady charges that Kessler's current "hunt-and-peck approach" of targeting big companies is largely an effort to shine up the FDA's tarnished image.

The agency surely needs better public relations—and much more. A report issued last week by an advisory panel to the Department of Health and Human Services concludes that the FDA is underfunded, understaffed and overwhelmed by its mandate, which ranges from approving drugs and monitoring the nation's blood supply to checking food imports and regulating the cosmetics industry. From 1979 to 1988, 23 laws were passed that broadened the FDA's responsibilities; at the same time, the agency lost 900 of its 8,100 employees.

That slide may finally be over. Congress has boosted the agency's budget by $150 million in the past two years, to $682 million for 1991, and the number of staff positions is up again to about 8,400. With that backing, Kessler hopes to strengthen the FDA in all areas. By picking on big food companies sensitive to publicity, he has made an astute start at establishing himself—and re-establishing the FDA—as the nation's top health cop. —*Reported by Dick Thompson/Washington and Linda Williams/New York*

In just five months, FDA chief Kessler has begun to restore public faith in an agency plagued by underfunding and overwork

WHAT'S WRONG WITH THESE LABELS?



JAMES KEYSER FOR TIME

It's misleading: the words "no cholesterol" stripped across a heart imply that this vegetable oil is healthy for the heart. True, it does not contain cholesterol, but, more important, vegetable oils are pure fat, and too much of that hurts the heart.

KEYSER

It's false: the pasta sauce touts itself as "fresh." That may describe the taste, but certainly not the preparation. In fact, the sauce is a precooked concoction of processed tomatoes and spices.

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The Battle of the Bureaucrats

■ Agencies: Rivals USDA and FDA have new leaders with contrasting styles that could have profound effects on the safety of the U.S. food supply.

[illegible] P. PUZO
[illegible] WRITER

The two most important federal agencies dealing with the nation's food supply have new leadership, and in recent weeks they have sent out dramatically contrasting signals.

Agriculture Secretary Edward R. Madigan entered office in March and killed an innovative nutrition education program at the request of farm commodity groups, thereby reinforcing a widely held perception that USDA frequently bows to industry wishes.

Meanwhile, over at the U.S. Food and Drug Administration, commissioner David A. Kessler MD took up his post in January and began waging a high-profile campaign against false health claims on food labels. His targets were the misuse of the terms *fresh* and *no cholesterol;* his actions angered major manufacturers and industry trade groups.

FDA and USDA, whose responsibilities frequently overlap, are long-time rivals for federal funding and frequently compete over turf. There is especially intense competition between FDA and the USDA's Food Safety and Inspection Service, which oversees the nation's meat and poultry industries. Both agencies are battling for control of what is expected to be a $100-million seafood inspection program. FSIS and FDA are also wrestling over which agency's nutritional labeling regulations will be adopted for use on all food products.

The conflicts are inevitable because of the tangled jurisdictions between the agencies. USDA, a huge department composed of more than 40 agencies, is charged with *promoting* agriculture and is responsible for all meat and poultry products. FDA, a single component of the U.S. Department of

AL STEPHENSON / For The Times

USDA'S Edward R. Madigan

When two new leaders were stirred into this mixture of turf battles, elusive funding and public criticism, those familiar with both agencies were eager to reveal their first impressions. Secretary Madigan, 55, is a former Republican congressman from Illinois. Commissioner Kessler, 39, is a physician, lawyer and academician. A veteran Washington observer remarked that the difference was striking. "Kessler hit the ground running, while Madigan hit the ground and stayed there," he said.

Predictably, consumer advocates laud Kessler's crackdown on misleading food labels and complain about Madigan's "cave-in" on the Eating Right Pyramid, which emphasized consumption of grains and produce at the expense of meat and dairy products. On the other hand, industry representatives have applauded Madigan's cautiousness and attacked Kessler's "grandstanding."

"Secretary Madigan shot himself in the foot by caving in to the meat and dairy industries [over his cancellation of the Eating Right Pyramid]," said Michael Jacobson, executive director of the Center for Science in the Public Interest in Washington. "I think he has undermined his credibility with the public. USDA [remains] a cheerleader for the industries it is

[the Eating Right Pyramid] done prior to his arrival and he decided he needed to study it some more, Cady said. "He is trying to do what is right and decide what is the proper manner in which to present the four food groups."

A different viewpoint on [illegible] and FDA is offered by Ellen [illegible], executive director of Public [illegible] for Food and Health Policy in Washington. She is not so quick to praise Kessler nor dismiss Madigan.

While complimenting Kessler's aggressiveness on false label claims, Haas said that the new FDA commissioner grasped "easy issues" that were already resolved in Congress by the passage of the Nutrition Labeling and Education Act in 1990. She also points out that there were significant segments of the food industry—and not just consumer groups—that wanted the government to crack down on misleading food labels and advertisements.

"[Kessler] has not changed direction from the passive player that the entire [FDA] has been," she said. "The real measure of his performance will be how he ensures the safety and wholesomeness of food. On this issue, we have not seen his colors, his bite or his teeth."

While conceding that Madigan made the wrong decision in withdrawing the Eating Right Pyramid, Haas said that he should not be judged on that issue alone.

"To preemptively withdraw the pyramid when meat interests complain leaves the action open to some hasty conclusions. Madigan didn't think of the political consequences, and he underestimated the concern of the nutritional community," Haas said. "But Madigan needs to make up for the poor start and he has the opportunity to do so."

The group most frequently mentioned as having urged Madigan to drop the Eating Right Pyramid was the National Cattlemen's Assn. A representative of the Denver-based group said the cattlemen's role has been exaggerated in press reports.

"All we did was tell [USDA] the concerns that we had,

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R. Madigan entered office in March an [illegible] innovative nutrition education program at the request of [illegible] commodity groups, thereby reinforcing a widely held perception that USDA frequently bows to industry wishes.

Meanwhile, over at the U.S. Food and Drug Administration, commissioner David A. Kessler MD took [illegible] post in January and [illegible] a high-profile campaign against false health claims on food labels. His targets were the misuse of the terms *fresh* and *no cholesterol*; his actions angered major manufacturers and industry groups.

FDA and USDA, whose responsibilities frequently overlap, are [illegible] rivals for federal funding and [illegible] compete over [illegible] especially intense competition between FDA and the USDA's Food Safety and Inspection Service, which oversees the nation's meat and poultry industries. Both agencies are battling for control of what is expected to be a $700-million seafood inspection program. FSIS and FDA are also wrestling over which agency's nutritional-labeling regulations will be adopted for use on all food products.

The conflicts are inevitable because of the tangled jurisdictions between the agencies. USDA, a huge department composed of more than 40 agencies, is charged with *promoting* agriculture and is responsible for all meat and poultry products. FDA, a single component of the U.S. Department of Health and Human Services, is empowered to *protect* the public's health and is responsible for all other foods, including monitoring for pesticide residues, combatting microbiological contaminants, evaluating the safety of additives and inspecting imported food.

According to a recent General Accounting Office report, both FDA and USDA have less funding, less staff and more work than 10 years ago.

"Available data show that the resources of the agencies have decreased since 1980 while their work loads related to food safety and quality have increased," the GAO reported.

Supporting the GAO's finding was a study by a federal advisory committee on FDA. The 15-member group found that the agency's current condition posed the "risk of impending public health catastrophe." The committee also recommended that FDA be given independent status similar to the Environmental Protection Agency, but the suggestion was immediately dismissed by Bush Administration officials.

AL STEPHENSON / For The Times

USDA'S Edward R. Madigan

When two new leaders were stirred into this mixture of turf battles, elusive funding and public criticism, those familiar with both agencies were eager to reveal their first impressions. Secretary Madigan, 55, is a former Republican congressman from Illinois. Commissioner Kessler, 39, is a physician, lawyer and academician. A veteran Washington observer remarked that the difference was striking. "Kessler hit the ground running, while Madigan hit the ground and stayed there," he said.

Predictably, consumer advocates laud Kessler's crackdown on misleading food labels and complain about Madigan's "cave-in" on the Eating Right Pyramid, which emphasized consumption of grains and produce at the expense of meat and dairy products. On the other hand, industry representatives have applauded Madigan's cautiousness and attacked Kessler's "grandstanding."

"Secretary Madigan shot himself in the foot by caving in to the meat and dairy industries [over his cancellation of the Eating Right Pyramid]," said Michael Jacobson, executive director of the Center for Science in the Public Interest in Washington. "I think he has undermined his credibility with the public . . . USDA [remains] a cheerleader for the industries it is supposed to oversee."

Jacobson, however, had praise for Kessler.

"He [Kessler] is a breath of fresh air in an agency where there was stale air for so many years. I hope this indicates a pattern of strong enforcement and an effort to stop companies from lying to the public [on product labels and advertisements]," Jacobson said. "He is reinvigorating the agency and reestablishing credibility with Congress, the public and the food industry."

Jacobson's opinions were certainly not echoed at the National Food Processors Assn., a Washington-based trade group.

Association president John R. Cady was highly critical of Kessler's methods, charging the commissioner with "regulating through the press."

"FDA should focus on the larger issues confronting the agency and stop this 'hunt and peck' approach . . . with [food labels]," Cady said.

As for USDA, Cady was more understanding of Madigan's situation.

"USDA had a new secretary [illegible] Act in 1990. She also points out that there were significant segments of the food industry—and not just consumer groups—that wanted the government to crack down on misleading food labels and advertisements.

"[Kessler] has not changed direction from the passive player that the entire [FDA] has been," she said. "The real measure of his performance will be how he ensures the safety and wholesomeness of food. On this issue, we have not seen his colors, his bite or his teeth."

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The group most frequently mentioned as having urged Madigan to drop the Eating Right Pyramid was the National Cattlemen's Assn. A representative of the Denver-based group said the cattlemen's role has been exaggerated in press reports.

"All we did was tell [USDA] the concerns that we had, such as the pyramid would give the consumer the idea that red meat was bad," said Alisa Harrison, information director of the National Cattlemen's Assn.'s Washington office. "It is presumptuous to say that we single-handedly stopped it."

Others did not believe the meat industry's role in the controversy was minimal.

"Madigan is another in a long line of people who reflect a philosophy that the Department of Agriculture should belong to the people that produce and process food and to hell with the people that eat," said Carol Tucker Foreman, a Washington public policy consultant who was a top USDA official in the Carter Administration. "It is really just the department of agribusiness and food processors."

Foreman applauded Kessler's recent decisions on food labeling and said that the uncharacteristic action is a positive sign for federal food regulation.

"The Bush Administration is taking some meaningful steps away from the Reagan Administration philosophy that all govern-

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127TH STORY of Level 2 printed in FULL format.

Proprietary to the United Press International 1991

April 11, 1991, Thursday, BC cycle

SECTION: Washington News

LENGTH: 559 words

HEADLINE: FDA needs dramatic overhaul, report says

BYLINE: BY JANET BASS

DATELINE: WASHINGTON

KEYWORD: FDA

BODY:

The Food and Drug Administration is unable to handle its current task of safeguarding the nation's food and drug supply, an expert panel concluded in a draft report released Thursday.

A panel convened by Health and Human Services Secretary Louis Sullivan to review the FDA's mission said it found the agency to be plagued by staff shortages, outdated equipment and lack of regulatory authority.

''It is glaringly apparent t the FDA cannot now execute all of its statuatory responsibilities within limitations of existing resources,'' stated the committee's draft report.

''Although the FDA has routinely lived with controversy, the magnitude of current pressures is unprecedented in nature and scope,'' it said, noting constant demands and scrutiny by consumer organizations and the media.

''The FDA is not currently prepared to cope with this environment (and) ... it is imperative that the agency better prepare itself for the future.''

The draft was under discussion at the panel's meeting Thursday and Friday in Washington. A final version is due to be delivered to Sullivan May 15.

Some critics have called for removing the FDA from HHS jurisdiction and setting it up as a cabinet-level agency like the Environmental Protection Agency.

However, the report only recommends removing FDA from under the Public Health Service's bureaucratic umbrella and having it report directly to HHS. The report said the change would acknowledge the vital importance of strengthening the FDA's law enforcement responsibilities.

''Moreover, it would demonstrate that the administration recognizes the importance of FDA's mission,'' it said.

But the panel said if the change is not accomplished promptly, establishing FDA as a free-standing agency independent of HHS ''deserves further consideration.''

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Proprietary to the United Press International, April 11, 1991

FDA Commissioner David Kessler, who was a member of the advisory committee until being named head of the agency in February, said he supports the recommendation that the FDA be given the power to issue supoenas, seize products and impose civil fines on firms that violate FDA regulations.

The FDA currently is reeling from a bribery scandal in its generic drug division and reports of a grand jury investigation into illegansider trading. In addition, AIDS activists have attacked the FDA's slowness in moving drugs to market, while consumer advocates charge the agency has done a poor job of protecting the public from health hazards like pesticides in foods and silicone breast implants.

The 15-member panel concluded FDA lacks adequate scientific ability to evaulate new drugs, let alone keep abreast with ''revolutionary advances occuring in biological and medical sciences.''

''Many of these (FDA) facilities are abysmal -- overcrowded, poorly maintained, hazardous and inefficient. Much of their scientific equipment is obsolete and technologically inadequate'' the report said..

Staffing shortages are another woe, leading to some food companies being inspected only once every seven or eight years and key steps being omitted from inspections of drug firms.

''Inspections have dropped by at least 40 percent over the past decade,'' the report said, adding that the number of seizures, injunctions and prosecutions of food and drug firms has also declined sharply since the 1970s.

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Exhibit H

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April 12, 1991, Friday, ALL EDITIONS

SECTION: NEWS; Pg. 17

LENGTH: 572 words

HEADLINE: Study: More Money, Power for FDA

BYLINE: By Michael Unger. STAFF WRITER

KEYWORD: FEDERAL FOOD AND DRUG ADMINISTRATION; BUDGET; INCREASE; RESEARCH; SAFETY; INVESTIGATION; SURVEY

BODY:

The federal Food and Drug Administration should have more financial and scientific resources to successfully regulate the growing array of new drugs, foods, cosmetics and medical devices, an advisory panel said in a draft report released yesterday.

"It is glaringly apparent that the FDA cannot now execute all of its statutory responsibilities within the limitations of existing resources," said the report, prepared by 15 experts chosen by the agency. The FDA employs 8,400 people to regulate the safety and effectiveness of products that account for 25 cents of every consumer dollar spent in the United States.

"It is essential that the FDA avoid being repeatedly blindsided by rapid advances in biomedical science and technology," the committee warned. "In a world undergoing rapid and significant scientific and technological change," including bioengineered and software-dominated products, the report said, the FDA "must better manage its research operations" and recruit and retain sorely needed scientific talent.

The panel is headed by Dr. Charles Edwards, who was the FDA commissioner from 1969 to 1973 and is now president of the Scripps Clinic and Research Foundation in La Jolla, Calif. It includes industry officials and representatives of consumer groups, scientists and physicians. The FDA's new commissioner, Dr. David A. Kessler of New York, was a member of the committee until he took office this year.

The Bush administration had no immediate comment on the report, which called for Health and Human Services Secretary Louis Sullivan to restore enforcement powers blocking the distribution of questionable goods and punishing the producers. That power was taken from the FDA commissioner by the Reagan administration in 1981. The commission also urged that the FDA be upgraded and given increased independence within the Health and Human Services Department from its position of what it called "a third-tier agency" in the U.S. Public Health Service.

Congressional Democrats said they were studying the recommendations.

The report drew a picture of a demoralized and floundering regulatory agency. The "FDA had a difficult time describing to the committee its current research

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activities, its goals, and the links between research projects and regulatory goals, which does not speak well for its management," it said.

The enforcement picture also was painted as bleak. "The evidence suggests the FDA is able to monitor a smaller share of the production, distribution, and sale of regulated products than a decade ago," the report said. The number of FDA field inspectors returned to 1979 levels only within the past year.

"The number of formal court enforcement actions brought by the agency - seizures, injunctions and prosecutions - has declined sharply since the 1970s. Inspections have also dropped by at least 40 percent over the past decade," the committee said.

While the number of domestic FDA-regulated products and establishments subject to inspection, such as pharmaceutical concerns, has increased, the FDA also has become responsible for inspecting a steadily rising number of imported foods, cosmetics and medical products. The FDA was strongly criticized for the way it handled the investigation of Chilean grapes said to be poisoned. Eventually, the agency came up with two poisoned grapes and temporarily suspended all shipments. No other poisoned grapes were found.

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Exhibit I

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considered in other states and Congress as the nation confronts spiraling health costs and widening gaps in the insurance system.

The plan's centerpiece — a requirement that businesses employing six or more workers offer them health insurance or pay the state to do it — was originally scheduled to take effect next January. But it now seems unlikely to materialize for years, if ever. The new Governor, William F. Weld, a conservative Republican, has asked the state legislature to repeal it, calling the requirement "an obstacle rather than a vehicle for improved health benefits for all."

Hard to Reach Consensus

Here as elsewhere, nearly all larger companies offer health insurance but many small and low-wage businesses do not, leaving many workers and their families

peal would send to other states," said State Representative John E. McDonough, a Boston Democrat who is a main supporter of the plan. "It's being killed not because of the design of the program but for political reasons, and because of a recession."

Opponents say that in the absence of other measures to control soaring medical and insurance costs, the plan would place crushing burdens on fragile businesses and a broke state government, and put the state's economy at a competitive disadvantage.

"Just mandating something doesn't make it work," said Charles Baker, the new Under Secretary for Health. "I'd rather try to get at the root causes of the problem through hospital financing and the insurance system. We can try to lower the cost of insur-

Continued on Page A16, Column 1

Panel Calls Federal Drug Agency Unable to Cope With Rising Tasks

By ROBERT PEAR
Special to The New York Times

WASHINGTON, April 10 — A Federal advisory committee appointed to study the Food and Drug Administration says the agency is overwhelmed and incapable of coping with vastly increased duties caused by the AIDS epidemic, a flood of food imports and advances in medical science and technology.

In a draft of its final report, the panel of 15 experts says that F.D.A. laboratories and equipment are in abysmal condition, that some food factories are inspected only once every eight years and that the agency no longer has adequate scientific ability to evaluate new drugs, much less to keep up with "revolutionary advances occurring in the biological and medical sciences."

The report says many of the F.D.A.'s problems can be traced to its relatively lowly status in the Federal hierarchy: It is one of many agencies in the Public Health Service, all of which report to an assistant secretary at the Department of Health and Human Services. The commission is urging that the F.D.A. be granted independent status within the Department of Health and Human Services, a move that would allow the F.D.A. Commissioner much greater authority to issue regulations and enforce them.

The draft report says the agency needs additional staff and equipment to perform its mission properly, but the report does not specify the cost. Nor does it say whether the Government should levy a fee on food and drug companies to augment the agency's budget, as the Bush Administration has proposed.

The Administration supports efforts to increase the agency's law-enforcement powers but opposes removal of the agency from the Public Health Service, saying that would hinder its cooperation with other units of the service, like the Centers for Disease Control.

Dr. Louis W. Sullivan, Secretary of the Department of Health and Human

Continued on Page B11, Column 1

INSIDE

tery. Then, through their first hours of forever, she wept.

"That is how they will eradicate us, piece by piece," said Ahmad Ali, an engineer from the northern Iraqi city of Dohuk. "Yesterday, maybe it was six dead, the day before three, tomorrow five."

Thick Mud and Scant Supplies

"It grows," he said. "Maybe after a week or 10 days, we will all be dead."

Ten days have passed since the Kurdish exodus from Iraq began reaching Biblical dimensions. Yet rescue operations, at least in this stretch of mountainous border where 100,000 or more Kurds have sought sanctuary, have yet to be translated into anything more concrete than a chaos of promises and intentions.

There is a Turkish relief effort, to be sure, bolstered by overseas contributions and aimed at hundreds of thousands of refugees massed at several entry points along the 206-mile frontier between Turkey and Iraq. American, British and French cargo planes have augmented that aid for the last four days by dropping bundles of emergency supplies to Kurds on both sides of the border.

How Many Physicians? None

But at this remote outpost, up steep paths of thick mud inaccessible to most trucks, it is hard to see a pattern to the haphazard distribution of what thus far have been meager food and water supplies. And any internal organization by the Kurds seems nonexistent.

"The snow is our water," a woman said. She and other refugees scoop up the snow that streaks the mountain's upper reaches, and boil it or simply let it melt. As for food, sometimes there is bread or potatoes, but far more often not. The more provident among the Iraqis hauled flour with them to make

Continued on Page A10, Column 3

New U.S. Warning to Iraq

Baghdad was told to avoid military operations in northern Iraq, where an international relief effort for Kurdish refugees is under way. Page A10.

An Iraqi Kurd r carried America

Officers To Prot

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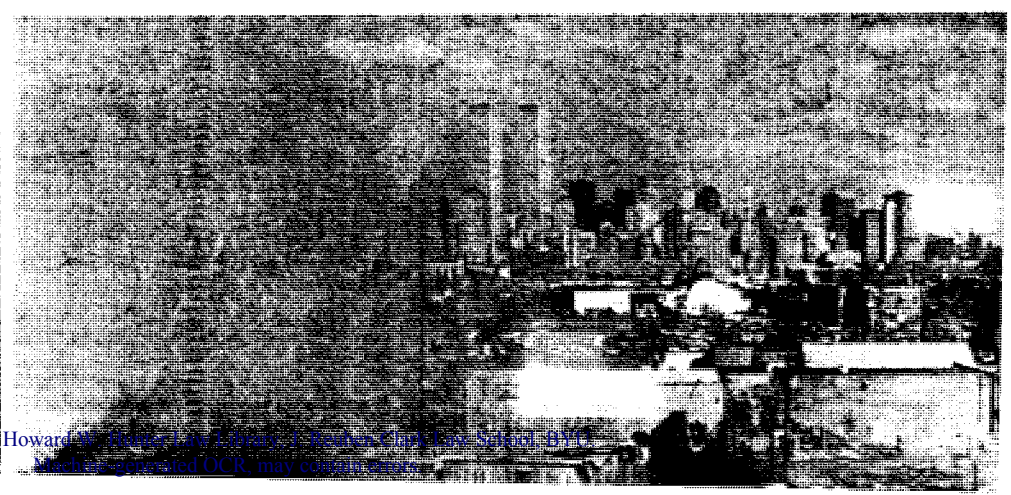

NEW YORK TIMES, APRIL 11, 1991, PG.A1

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U.S. Panel Sees Drug Agency as Unable to Cope With Rising Tasks

Continued From Page A1

Services, has publicly denounced proposals to remove the F.D.A. from his department, and department officials said tonight that he was also cool to the idea of removing it from the Public Health Service. However, Congress could make such changes by legislation. Democratic lawmakers, including Representative John D. Dingell of Michigan, chairman of the Energy and Commerce Committee, which supervises the F.D.A., have said the agency needs more independence.

Regulating Soup to AIDS Drugs

The agency is charged with regulating products that account for 25 cents of every dollar spent by American consumers — everything from soup to nuts, from suntan lotion to tomatoes and ice cream, from eyedrops and hearing aids to artificial heart valves, AIDS drugs and shampoo. In recent years, the panel said, the agency has had to deal with a "dramatic growth in imported foods," often from countries with minimal food safety standards.

But the advisory panel, appointed by Dr. Sullivan, said the F.D.A. Commissioner lacks the authority to perform important duties, so that Federal laws are not fully or properly carried out.

"It is glaringly apparent that the F.D.A. cannot now execute all of its statutory responsibilities within the limitations of existing resources," the panel says, and it warns that "nonenforcement invites violations from unscrupulous firms."

For years, the F.D.A. Commissioner had authority to issue all regulations carrying out the laws for which the agency was responsible. But in 1981, the Reagan Administration sharply limited this authority, insisting that the Commissioner first get approval from the Secretary of Health and Human Services and from the Assistant Secretary for health. The advisory panel said that Secretary Sullivan should reinstate the Commissioner's power to issue rules.

"This single step would do more than any other measure available to the department to restore the Commissioner's prestige" and to increase the effectiveness of the F.D.A., it said.

Fewer Inspections

"The number of formal court enforcement actions brought by the agency — seizures, injunctions and prosecutions — has declined sharply since the 1970's," said the panel. "Inspections have also dropped by at least 40 percent over the past decade."

The panel, the Advisory Committee on the Food and Drug Administration, is headed by Dr. Charles C. Edwards, who served as F.D.A. Commissioner from 1969 to 1973 and is now president of the Scripps Clinic and Research Foundation in La Jolla, Calif. The panel includes representatives of consumer groups, food and drug executives, doctors, scientists and five former F.D.A. officials.

The F.D.A. has been plagued with troubles in recent years, going for 14 months without a permanent Commissioner and suffering a scandal involving payments to influence approval of generic drugs.

The agency "cannot adequately enforce all the requirements in its laws and regulations," the panel concludes. Accordingly, it says, "dramatic steps must be taken to enlarge F.D.A.'s status and independence."

The committee will meet here on Thursday and Friday to review its final report, and it expects to present the document to Dr. Sullivan on May 15. Richard A. Merrill, former chief counsel of the agency and a member of the advisory panel, said the draft reflects "the consensus position of the committee," including "conclusions we have reached at successive meetings" and hearings over the last year.

The panel's recommendations, which also call for more vigorous enforcement of laws and regulations, are notable because 6 of the 15 committee members come from companies or industries regulated by the F.D.A. Consumer groups have complained for years that the agency was a sleepy watchdog.

The advisory committee observed that "some food firms are inspected only once every seven or eight years." Moreover, it said, even though drug companies are inspected more frequently, "elements essential to a thorough inspection have to be omitted" because of personnel shortages at the agency.

The F.D.A. Commissioner, now reports to the department's assistant secretary for health, Dr. James O. Mason, who also supervises other branches of the Public Health Service, including the National Institutes of Health, the Centers for Disease Control and the Indian Health Service.

Dr. Mason contends that the F.D.A. should keep its current position in the Federal bureaucracy so it can coordinate its work closely with other components of the Public Health Service.

The current Commissioner of Food and Drugs, Dr. David A. Kessler, was a member of the advisory committee until he became head of the F.D.A. in February. He said he supports the panel's recommendations to give the agency expanded powers to issue subpoenas, seize products and impose civil monetary penalties on companies that violate F.D.A. regulations.

Obsolete Equipment

In its report, the advisory committee expresses alarm at the deterioration of laboratories and equipment used to assess the safety of food, drugs and medical devices.

"In the Washington, D.C., area, the F.D.A. occupies more than 32 buildings in 11 different locations," it says. "Many of these facilities are abysmal — overcrowded, poorly maintained, hazardous and inefficient. Much of their scientific equipment is obsolete and technologically inadequate."

The panel expresses concern that many states, perceiving the F.D.A. as sluggish and unresponsive, are adopting food and drug standards beyond those enforced by the Federal Government, so that national uniformity is often compromised. In recent years, consumer groups say they have found some states, like California, more aggressive than the F.D.A. in trying to protect consumers.

In a recommendation subject to further review by panel members, the draft report says, "Congress should enact legislation that pre-empts additional and conflicting state requirements for products regulated by F.D.A." However, it says that states should be allowed to get an exemption from uniform national standards if they can prove a compelling local need.

The panel acknowledges that Congress is unlikely to give the agency a big budget increase at a time when the Federal budget deficit is approaching $300 billion.

We're Changing Our Ways, With Nonstop Service To Both São Paulo And Rio.

Miami

Miami

Books of The Times

NEW YORK TIMES, APRIL 11, 1991, PG. B11

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Exhibit J

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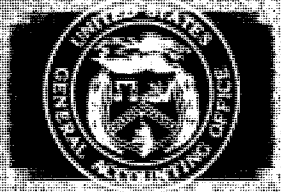
United States General Accounting Office

GAO

Report to the Chairman, Subcommittee on Human Resources and Intergovernmental Relations, Committee on Government Operations, House of Representatives

FDA DRUG REVIEW

Postapproval Risks 1976-85



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GAO
United States
General Accounting Office
Washington, D.C. 20548

Program Evaluation and
Methodology Division

B-235944

April 26, 1990

The Honorable Ted Weiss
Chairman, Subcommittee on Human Resources
and Intergovernmental Relations
Committee on Government Operations
House of Representatives

Dear Mr. Chairman:

In response to your request, we are submitting this report describing postapproval risks for drugs approved by the Food and Drug Administration between 1976 and 1985. The report identifies drugs for which serious risks arose after approval for marketing, and it investigates the relationship of these risks to some attributes of the drugs and the review process.

As we arranged with your office, unless you publicly announce the contents of this report earlier, we plan no further distribution of it until 30 days from the date of the report. At that time, copies of the report will be sent to the Secretary of the Department of Health and Human Services and the Commissioner of the Food and Drug Administration, and we will make copies available to others upon request.

If you have any questions or would like additional information, please call me at (202) 275-1854 or Dr. Michael J. Wargo, Director of Program Evaluation in Physical Systems Areas, at (202) 275-3092. Other major contributors to this report are listed in appendix VI.

Sincerely,

Eleanor Chelimsky
Assistant Comptroller General

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Executive Summary

Purpose

Assessing the efficacy and safety of a drug to obtain Food and Drug Administration (FDA) approval is a lengthy and complex process. But even after approval, many additional risks may surface when the general population is exposed to a drug. These risks, which range from relatively minor (such as nausea and headache) to serious (such as hospitalization and death) arise from the fact that preapproval drug testing is inherently limited. The extent of postapproval risks and the reasons they go undetected during preapproval testing, however, have not been analyzed.

The Chairman of the Subcommittee on Human Resources and Intergovernmental Relations of the House Committee on Government Operations asked GAO to study the frequency and seriousness of drug risks identified after FDA approval for marketing and to examine some of the characteristics of these drugs as a first step in understanding why these additional risks occur.

Background

The drug approval process begins with the submission of an "investigational" application, when a drug company applies to FDA for permission to test the drug in humans. Then, when the clinical studies involving humans provide evidence of a particular drug's beneficial effect at an acceptable level of safety, the company submits a new drug application (120 were submitted in 1986) to FDA for approval of the drug for widespread use. The agency subsequently reviews all evidence pertaining to the drug's efficacy and safety. If it finds the cumulative evidence acceptable, FDA approves the drug for marketing (after, on the average, 29 months of review).

The preapproval human clinical trials for a drug involve testing with a relatively small sample of the potential user population under controlled conditions that limit the extent of risk assessments. However, when therapeutic benefits appear to outweigh the estimated potential risks, the new drug is approved as soon as possible for the benefit of those who can use it. After FDA approves the drug for marketing, it is then used by patients under conditions much less controlled than those that prevailed during testing.

When a company markets an approved drug, it is required by law to include directions for its use—as well as warnings, precautions, and adverse reactions—on the drug's label. Postmarketing surveillance then identifies potential adverse reactions not included on the original label that are discovered after marketing is begun. If an adverse reaction is

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Summary and Recommendation

Our analyses of almost all new drugs approved by FDA between 1976 and 1985 provide a broader perspective on the magnitude of postapproval drug risks than it is possible to obtain from considering the development and approval of an individual drug or from considering the efficiency of the drug review process. The information and analyses we contribute here have not been previously available. The findings suggest that it would be worthwhile for FDA to build upon our results.

ummary

In chapter 2, we showed that 51.5 percent (102) of the 198 drugs we analyzed had serious postapproval risks as evidenced by labeling changes or withdrawal from the market. Several pharmacologic classes had a much higher percentage of drugs with serious postapproval risks, while other classes had a much smaller percentage. This finding indicates that the class of a drug is associated with the likelihood of serious postapproval risks.

We found that there was considerable concentration of the serious postapproval risks for certain disease categories and drug classes (frequently between three and five categories for an individual drug). We also showed that serious postapproval risks are frequently more serious manifestations of adverse effects known at the time of approval. These findings can be useful in predicting postapproval risks during the drug review process and in postmarketing surveillance.

We showed in chapter 3 that examination of several drug characteristics provided insights that can inform the drug review process and policy issues pertaining to drug approval and postmarketing surveillance. In particular, we found that drugs reviewed for use with children were over twice as likely to have serious postapproval risks and that drugs appearing on FDA's MART list were over 10 times as likely to have serious postapproval risks. We showed that drugs with serious postapproval risks had a shorter approval time than drugs without such risks. We found that there is a greater time lag (perhaps over 5 years) than expected (less than 3 years) between a drug's approval, the reporting of adverse reactions, and the subsequent changing of labels. Although these findings are not conclusive, we believe they raise questions that deserve further attention.

ecommendation

We recommend that the Commissioner of FDA establish formal systemic procedures to assure that serious risks identified after a new drug has been approved are evaluated and used to enhance premarketing review

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of clinical trials and postmarketing surveillance of adverse reactions. We believe that the implementation of such procedures would, over the long run, contribute to better and more timely labeling, in both the review process and postmarketing surveillance.

We believe that FDA should, in implementing this recommendation, build upon the results developed in chapter 2, including

- identification of drugs with postapproval risks, characterized as serious and nonserious;
- enumeration of the serious postapproval risks by drug class, identifying any "class labeling" changes;
- enumeration of the serious postapproval risks by drug-induced disease category, indicating whether the category is newly identified for the drug or is an extension of less severe adverse reactions already identified for the drug and tabulating the number and type of disease categories by drug and drug class; and
- comparison of the serious and nonserious postapproval risks with the serious and nonserious risks identified at the time of approval.

For developing a system for capturing and analyzing postapproval risk information, we also suggest that FDA make an effort to introduce more quantitative risk analysis methods. To support such methods, the following kinds of information would be needed about a given drug:

- the number of people exposed to the drug,
- the proportion likely to be affected by the risk either for the general population or for specific subpopulations,
- indicators reflecting the relative significance of fatalities and morbidity (including hospitalization, prolonged hospitalization, and permanent or temporary disability), and
- the time period over which the population is exposed to the risk.

We believe this additional information would improve the understanding of postapproval risks, presenting a more definitive basis for identifying trends and informing the need for safety information prior to approval.

Agency Comments and Our Response

HHS did not concur with our recommendation as stated in the draft report. We have clarified it and more fully explained the rationale for our position. We have also rearranged the text to make specific implementation steps clearer.

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Exhibit K

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Given the passage of time, are the dangers of falsely inferring an original defect from the fact of a subsequent defect—a defect present in the product at the time of accident—sufficient to justify a statute of repose? How should the law respond when that subsequent defect is explainable in terms of the deterioration of the product over time?

A malfunction in a product at some time after product purchase will often properly support a finding of original defect. If a malfunction theory should therefore be recognized, it should also be delimited. For example, a satisfactory post-malfunction inspection of the product may rule out a credible defect finding. The malfunction theory is most convincing when the product has been destroyed in the accident itself and when the passage of time between product sale and product malfunction is meaningfully short.

The problem of manufacturer liability for product deterioration has impressed many observers as a considerable mystery. A solution to the mystery may be found in the standard classification of product defects, which identifies the circumstances in which deterioration should be suggestive of manufacturer liability. Not to be overlooked, however, are the significant responsibilities, and hence liabilities, that an intelligent law should place on the shoulders of the product owner.

The question of a statute of repose for product liability claims is provocative. Many possible explanations for such statutes—for example, that prolonged safe use categorically demonstrates nondefectiveness—do not survive analysis, though there may be particular theories of original defect that prolonged safe use succeeds in eliminating. A statute of repose is certain to result in the denial of a significant number of valid claims, denials that seem both imperfectly fair and disadvantageous in terms of deterrence. Yet repose statutes can be supported by tough-minded arguments relating to the overall expense of weak old-product claims. Thus far, however, the empirical basis for these arguments has not been demonstrated. From all one now can tell, an old-fashioned remedy like the directed verdict may be on balance as satisfactory as any of the new-fashioned alternatives.

GENERIC PRODUCT RISKS: THE CASE AGAINST COMMENT k AND FOR STRICT TORT LIABILITY

JOSEPH A. PAGE*

Professor Page considers whether strict liability should be imposed for injuries caused by products that pose generic risks—risks that do not derive from flaws in the manufacturing process but from product design or from the very nature of the product. He reviews the ALI debate that preceded adoption of section 402A of the Restatement (Second) of Torts and finds the ambiguous meaning of comment k, which deals with "unavoidably unsafe" products, of little use in determining whether section 402A applies to generic product risks. After examining the policy justifications for imposing strict liability in cases involving design defects and construction defects, Professor Page concludes that, at least in cases involving generic product risks that were unknown at the time of sale, strict liability should be imposed as a modest incentive to manufacturers to improve product safety and as a means of satisfying justifiable consumer expectations.

INTRODUCTION

Recent litigation involving asbestos[1] and DES[2] has attracted widespread interest, not only because of the staggering numbers of claimants alleging serious harm from these products[3] and the filing of a bankruptcy petition by the nation's largest asbestos manufacturer,[4] but also because of the complexity of the issues that the cases involve.

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The author gratefully acknowledges the assistance of Peter J. Cinquegrani, Class of 1984, Georgetown University Law Center.

[1] Asbestos has been implicated as a cause of asbestosis, lung cancer, mesothelioma (a cancer of the chest or abdominal lining), and various forms of gastrointestinal cancers. See Hazards of Asbestos Exposure: Hearings Before the Subcomm. on Commerce, Transportation, and Tourism of the House Comm. on Energy and Commerce, 97th Cong., 2d Sess. 2-11 (1982) (testimony of Dr. Irving Selikoff, Environmental Science Laboratory, Mt. Sinai Medical Center) [hereinafter Asbestos Hearings].

[2] DES, or diethylstilbestrol, is a synthetic estrogen that was prescribed routinely to pregnant women to prevent miscarriages. The Food and Drug Administration approved DES in 1947. In 1971 the drug was linked to a form of vaginal cancer in the daughters of women to whom it was administered. For a discussion of this history, see generally Payton v. Abbott Labs., 512 F. Supp. 1031, 1032-34 (D. Mass. 1981); Comment, DES and a Proposed Theory of Enterprise Liability, 46 Fordham L. Rev. 963, 963-68 (1978).

[3] It has been estimated that nine million American workers were exposed to asbestos during the 1940's and 1950's. See Asbestos Hearings, supra note 1, at 3 (testimony of Dr. Irving Selikoff). Estimates of the number of women who ingested DES range from three to four million. See Note, Market Share Liability: An Answer to the DES Causation Problem, 94 Harv. L. Rev. 668, 668 n.7 (1981).

[4] On August 26, 1982, Manville Corporation, the largest producer of asbestos in the western world, filed a petition for reorganization under the federal bankruptcy code. The company cited the projected cost of mounting asbestos litigation as the major reason for its filing a bankruptcy petition. See N.Y. Times, Aug. 27, 1982, at A1, col. 6; Wall St. J., Aug. 27, 1982, at 1, col. 6.

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For example, many DES claimants, daughters of women who took the drug during pregnancy, are unable to identify the maker of the particular pills consumed by their mothers. The courts have had to decide whether to depart from traditional causation rules that would require directed verdicts for defendants, and if so, what new rules to adopt.[5] In the asbestos cases, courts have had to determine the obligations of successive insurers to indemnify asbestos manufacturers against claims made by persons who allegedly contracted respiratory diseases from continuous exposure to asbestos over many years.[6] In addition to these problems, an array of legal theories asserted against an array of defendants who do not manufacture asbestos or DES has emerged in these cases.[7]

The few courts reaching the merits of claims made by asbestos and DES victims have, for the most part, refused to venture beyond the familiar confines of negligence law. Giving dispositive weight to

[5] Courts have reached opposite conclusions about whether plaintiffs who cannot identify the specific manufacturer of the drug to which they were exposed may recover. Compare Sindell v. Abbott Labs., 26 Cal. 3d 588, 610-13, 607 P.2d 924, 936-38, 163 Cal. Rptr. 132, 144-46 (recovery allowed under theory of market share liability), cert. denied, 449 U.S. 912 (1980); Ferrigno v. Eli Lilly & Co., 175 N.J. Super. 551, 567-69, 420 A.2d 1305, 1314-16 (Law Div. 1980) (recovery allowed under "alternative liability" theory); Bichler v. Eli Lilly & Co., 55 N.Y.2d 571, 584-85, 436 N.E.2d 182, 188-89, 450 N.Y.S.2d 776, 782-83 (1982) (recovery allowed under "concert of action" theory) with Morton v. Abbott Labs., 538 F. Supp. 593, 596-600 (M.D. Fla. 1982) (recovery denied); Mizell v. Eli Lilly & Co., 526 F. Supp. 589, 596-97 (D.S.C. 1981) (same); Payton v. Abbott Labs., 512 F. Supp. 1031, 1039-40 (D. Mass. 1981) (same). Since federal courts hear product liability cases only under diversity jurisdiction, each of the above district courts applied the appropriate state law. For a state court refusing to relax the traditional requirement that a plaintiff identify the defendant who actually caused the harm, see Payton v. Abbot Labs., 437 N.E.2d 171, 188-90 (Mass. 1982).

[6] Some courts have adopted a theory under which all companies that insured an asbestos firm during the period a claimant was exposed would contribute to the defense of the suit and to the satisfaction of an adverse judgment. See Keene Corp. v. Insurance Co. of N. Am., 667 F.2d 1034, 1050 (D.C. Cir. 1981) (adopting "exposure" theory of liability), cert. denied, 455 U.S. 1007 (1982); Porter v. American Optical Corp., 641 F.2d 1128, 1145 (5th Cir.) (same), cert. denied, 454 U.S. 1109 (1981); Insurance Co. of N. Am. v. Forty-Eight Insulations, Inc., 633 F.2d 1212, 1224-25 (6th Cir. 1980) (same), cert. denied, 454 U.S. 1109 (1981). For a decision requiring defense and indemnification only from the insurance company that covered the asbestos firm at the time the claimant's disease manifested itself, see Eagle-Picher Indus., Inc. v. Liberty Mut. Ins. Co., 523 F. Supp. 110, 115-17 (D. Mass. 1981) (adopting "manifestation" theory of liability), modified, 682 F.2d 12 (1st Cir. 1982).

[7] See, e.g., Porter v. American Optical Corp., 641 F.2d 1128 (5th Cir.) (action against manufacturer of respirator that failed to prevent asbestos-related disease), cert. denied, 454 U.S. 1109 (1981); Glover v. Johns-Manville Corp., 525 F. Supp. 894 (E.D. Va. 1979) (indemnity action by asbestos manufacturer against the United States as third-party defendant in suit by injured worker), aff'd in part, vacated and remanded in part, 662 F.2d 225 (4th Cir. 1981); Mink v. University of Chicago, 460 F. Supp. 713 (N.D. Ill. 1978) (battery action against hospital for experimental use of DES).

section 402A of the Restatement (Second) of Torts, which imposes strict liability for "any product in a defective condition unreasonably dangerous to the user,"[8] and to comment k of section 402A, which recognizes an exception to strict liability for products deemed "unavoidably unsafe,"[9] these courts in effect have required plaintiffs to establish that defendants engaged in unreasonable conduct. Under this analysis, if the benefits of a product outweigh its known risks, and if the manufacturer has provided suitable warnings and directions for use, the defendant's product will be deemed reasonably safe, and the plaintiff will not recover.[10] Similarly, if the manufacturer has placed

[8] Restatement (Second) of Torts § 402A (1965) provides in full:

Special Liability of Seller of Product for Physical Harm to User or Consumer

(1) One who sells any product in a defective condition unreasonably dangerous to the user or consumer or to his property is subject to liability for physical harm thereby caused to the ultimate user or consumer, or to his property, if

(a) the seller is engaged in the business of selling such a product, and

(b) it is expected to and does reach the user or consumer without substantial change in the condition in which it is sold.

(2) The rule stated in Subsection (1) applies although

(a) the seller has exercised all possible care in the preparation and sale of his product, and

(b) the user or consumer has not bought the product from or entered into any contractual relation with the seller.

[9] Restatement (Second) of Torts § 402A comment k (1965) provides in full:

Unavoidably unsafe products. There are some products which, in the present state of human knowledge, are quite incapable of being made safe for their intended and ordinary use. These are especially common in the field of drugs. An outstanding example is the vaccine for the Pasteur treatment of rabies, which not uncommonly leads to very serious and damaging consequences when it is injected. Since the disease itself invariably leads to a dreadful death, both the marketing and the use of the vaccine are fully justified, notwithstanding the unavoidable high degree of risk which they involve. Such a product, properly prepared, and accompanied by proper directions and warning, is not defective, nor is it *unreasonably* dangerous. The same is true of many other drugs, vaccines, and the like, many of which for this very reason cannot legally be sold except to physicians, or under the prescription of a physician. It is also true in particular of many new or experimental drugs as to which, because of lack of time and opportunity for sufficient medical experience, there can be no assurance of safety, or perhaps even of purity of ingredients, but such experience as there is justifies the marketing and use of the drug notwithstanding a medically recognizable risk. The seller of such products, again with the qualification that they are properly prepared and marketed, and proper warning is given where the situation calls for it, is not to be held to strict liability for unfortunate consequences attending their use, merely because he has undertaken to supply the public with an apparently useful and desirable product, attended with a known but apparently reasonable risk.

(emphasis in original).

[10] See, e.g., Borel v. Fibreboard Paper Prods. Corp., 493 F.2d 1076, 1091 (5th Cir. 1973) (even when such a balancing leads to the conclusion that marketing is justified, the seller still has a responsibility to inform the user or consumer of the risk. The failure to give adequate warnings in such circumstances can render the product unreasonably dangerous." (citing comment k)), cert. denied, 419 U.S. 869 (1974); Ferrigno v. Eli Lilly & Co., 175 N.J. Super. 551, 559, 420 A.2d 1305, 1318 (Law Div. 1980) (comment k rules "are not strict liability rules at all. They are merely rules of negligence embodying the long-standing concepts of a lack of due care and foreseeability of the risk.").

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the product into the stream of commerce without knowledge of the dangers associated with its use or consumption, courts typically have refused to impose liability unless the exercise of reasonable care would have uncovered the hazards.[11] One notable exception to this trend is a recent decision by the New Jersey Supreme Court, holding that an asbestos producer might be strictly liable in tort for injuries caused by risks that were unknown despite reasonable investigation at the time of sale.[12]

The reluctance of courts to impose strict liability in toxic-product cases corresponds to a trend, reflected in scholarly musings[13] and adopted in recent congressional reform efforts,[14] to limit strict liability to product defects attributable to the construction or manufacturing process. With respect to claims alleging inadequate product design, warnings, or instructions for use, the proponents of this limitation would apply a negligence test, either expressly or in a disguised form.

Although the desirability of imposing strict liability upon the pharmaceutical industry for adverse drug reactions has been debated,[15] the larger issue of whether all manufacturers should be held liable without fault for other types of toxic adverse effects of their products largely has escaped scrutiny. Since courts in a number of jurisdictions may soon be addressing the merits of asbestos and DES cases, a fresh look at the subject seems in order.

The central focus of this Article is whether all "generic product risks" should be treated alike. The Article first will discuss the various types of generic risks—avoidable and unavoidable, known and unknown—including those risks associated with toxic products like asbestos and DES.[16] It will then argue that section 402A of the Restatement and its comments provide little guidance in deciding cases that involve generic risks, and should not be accorded dispositive weight in product liability suits. The Article will then examine and evaluate the policy justifications for adopting a rule of strict tort liability in cases involving generic risks. Ultimately, the Article will conclude that a persuasive case can be made for imposing strict liability on manufacturers whose products contain unknown generic risks.

[11] See, e.g., Borel v. Fibreboard Paper Prods. Corp., 493 F.2d 1076, 1090 (5th Cir. 1973) ("A product must not be made available to the public without disclosure of those dangers that the application of reasonable foresight would reveal."), cert. denied, 419 U.S. 869 (1974); Henderson, Coping With the Time Dimension in Products Liability, 69 Calif. L. Rev. 919, 924 (1981).

[12] See Beshada v. Johns-Manville Prods. Corp., 90 N.J. 191, 209, 447 A.2d 539, 546 (1982).

[13] See Birnbaum, Unmasking the Test for Design Defect: From Negligence to Warranty to Strict Liability to Negligence, 33 Vand. L. Rev. 593 (1980); Powers, The Persistence of Fault in Products Liability, 61 Tex. L. Rev. 777 (1983).

[14] See S. 44, 98th Cong., 1st Sess. §§ 5, 6, 129 Cong. Rec. S285 (daily ed. Jan. 26, 1983) (strict liability for unreasonably dangerous construction or manufacture; fault-based liability for unreasonably dangerous design or failure to provide adequate warnings or instructions); S. 2631, 97th Cong., 2d Sess., 128 Cong. Rec. S6846 (daily ed. June 16, 1982) (virtually identical predecessor version of S. 44).

[15] See generally McClellan, Tate & Eaton, Strict Liability for Prescription Drug Injuries: The Improper Marketing Theory, 26 St. Louis U.L.J. 1 (1981); Merrill, Compensation for Prescription Drug Injuries, 59 Va. L. Rev. 1 (1973); Pratt & Parron, Diagnosis of a Legal Headache: Liability for Unforeseeable Defects in Drugs, 53 St. John's L. Rev. 517 (1979); Note, The Liability of Pharmaceutical Manufacturers for Unforeseen Adverse Drug Reactions, 48 Fordham L. Rev. 735 (1980).

I

The Nature of Product Risks

Risks attributable to flaws or impurities caused by the manufacturing process usually are present only in a small percentage of the units of a particular product and do not endanger every consumer of the product. Such product risks are nongeneric in nature. The presence of a foreign substance in a jar of mayonnaise and a malfunction in a television set due to poor workmanship exemplify this category of hazards. In contrast, asbestos and DES share a common characteristic: the capacity to create risks that endanger, but do not necessarily harm, every user or consumer of the product. Such product risks are generic in nature.

This Article will focus on generic product risks, of which there are two main types. One includes design risks, or risks that can be eliminated or at least reduced by changing the design of the product. For instance, the interior of an automobile can be made more crashworthy so that the occupant is more likely to survive a collision. Some design risks, however, may be impossible to eliminate or to reduce without frustrating the purpose for which the product is marketed. The sharpness of a knife, the heat of a stove, and the physical force generated by an automobile are examples of this type of risk. These hazards enable the products to do what they were meant to do; they are essential to the function of the product and cannot be designed away.

The hazards associated with toxic products like asbestos and DES represent the second main type of generic risk. The manufacturers of asbestos products and DES have no desire to create the hazards associated with their products because these hazards serve no useful purpose. Unlike the capacity of a knife to cut, which is essential to its intended use, the capacity of DES to cause cancer in the daughters of

[16] Although generic risks associated with toxic products like asbestos and DES are but one type of generic risk, these products represent a particularly important type of generic risk.

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mothers who used the drug is irrelevant to the effectiveness of the drug; while the cutler consciously designs the cutting edge of a knife, the pharmaceutical company does not intentionally create the risk of cervical cancer. Toxic product risks are inherent in the nature of the product,[17] regardless of its design, and cannot be eliminated, at least given the current state of scientific knowledge, by any means short of withdrawing the product from the market.[18]

Other examples of generic, nondesign risks abound: adverse reactions to drugs and exposure to harmful chemicals;[19] the risk of cancer from smoking cigarettes;[20] the risk of "toxic shock" from using tampons;[21] and the possibly deleterious effects of consuming food and beverages containing saccharin[22] and caffeine,[23] if these substances were someday linked conclusively to diseases in humans.

As the saccharin and caffeine examples suggest, different types of generic risks, whether designed into a product or inherent in its nature, may also be distinguished by the degree of existing knowledge about them. Some generic risks, such as the risk of cancer from smoking cigarettes, are well known to manufacturers and consumers alike. Other generic risks, such as the carcinogenic effects of DES, were unknown when the consumer was exposed to them. Still others, such as the possible side effects of caffeine, remain unknown today.

[17] Nongeneric risks may also be inherent in a component part of a product. Indeed, it was a flawed wooden spoke on the wheel of a 1910 Buick that gave birth to modern product liability law. See MacPherson v. Buick Motor Co., 217 N.Y. 382, 111 N.E. 1060 (1916) (Cardozo, J.).

[18] In some instances, manufacturers can minimize the generic risks associated with their toxic products by providing consumers and users with warnings and instructions. For example, drug producers can warn users who might suffer allergic reactions, and asbestos producers can instruct users to use protective masks when installing asbestos insulation. Warnings and instructions can be used effectively, of course, only with respect to hazards that are known to exist.

[19] Representative recent cases involving these risks include Stiles v. Union Carbide Corp., 520 F. Supp. 865 (S.D. Tex. 1981) (vinyl chloride); Gutowski v. M & R Plastics & Coatings, Inc., 60 Mich. App. 499, 231 N.W.2d 456 (1975) (tolylenede-isocyanates); Peterson v. Bendix Home Sys., Inc., 318 N.W.2d 50 (Minn. 1982) (formaldehyde).

[20] Representative cigarette-cancer cases include Green v. American Tobacco Co., 391 F.2d 97 (5th Cir. 1968), cert. denied, 397 U.S. 911 (1970) (prior appeals reported in 325 F.2d 673 (5th Cir. 1963); 304 F.2d 70 (5th Cir. 1962)); Pritchard v. Liggett & Myers Tobacco Co., 350 F.2d 479 (3d Cir. 1965), cert. denied, 382 U.S. 987 (1966) (prior appeal reported in 295 F.2d 292 (3d Cir. 1961)); Lartigue v. R.J. Reynolds Tobacco Co., 317 F.2d 19 (5th Cir.), cert. denied, 375 U.S. 865 (1963).

[21] See Lampshire v. Procter & Gamble Co., 94 F.R.D. 58 (N.D. Ga. 1982). For a description of toxic-shock syndrome, see Robertson, Toxic Shock, N.Y. Times, Sept. 19, 1982, § 6 (Magazine), at 30.

[22] For a discussion of the dangers of saccharin use, see, e.g., The Banning of Saccharin, 1977: Hearing Before the Subcomm. on Health and Scientific Research of the Senate Comm. on Human Resources, 95th Cong., 1st Sess. 91-97 (1977) (testimony of Donald S. Fredrickson, Director, National Institutes of Health).

[23] For a discussion of the possible dangers of caffeine use, see N.Y. Times, Apr. 21, 1982, at C1, col. 1.

This Article discusses whether or not these various generic product risks—designed-in and inherent, known and unknown—should be treated alike for purposes of applying strict liability. Should the rights of a plaintiff whose hand is burned by a hot stove or whose eye is injured because a machine tool lacks a safety device be determined by the same theory of liability that determines the rights of a plaintiff disabled by exposure to toxic asbestos fibres or DES? Should the claim of a patient harmed by an adverse side effect known to be associated with a drug be governed by the same theory of liability as is the claim of a patient injured by an adverse side effect that was unknown at the time the drug was administered? The light shed on these questions by the Restatement (Second) of Torts, which has greatly influenced the development of product liability doctrine, is an appropriate starting point.

II

Generic Product Risks and the Restatement

Section 402A of the Restatement (Second) of Torts[24] gave impetus to a profound and far-reaching change in the law of product liability. It subjected sellers, including manufacturers, of all products to strict liability and grounded the cause of action in tort rather than warranty.[25] This change was important because a warranty cause of action was contractual in nature and was being preempted by the Uniform Commercial Code.[26] More importantly, this change relieved plaintiffs of the need to establish a privity-of-contract relationship with defendants. This so-called "citadel of privity," preventing plaintiffs from asserting breach of warranty against defendants with whom they were not in privity, already had almost totally collapsed in warranty cases involving products for internal human consumption, and was crumbling under the onslaught of plaintiffs injured by manufactured goods.[27] The widespread judicial adoption of section 402A

[24] See note 8 supra.

[25] See Restatement (Second) of Torts § 402A comment m (1965).

[26] The Uniform Commercial Code recognizes an implied warranty of merchantability running with the sale of goods, under which the goods must be fit for the ordinary purposes for which they are sold. See U.C.C. § 2-314 (1978). By 1965, the Uniform Commercial Code had been adopted in over 40 jurisdictions. See J. White & R. Summers, Uniform Commercial Code 5 (1972).

[27] The classic articles on the demise of the privity requirement were both written by Dean Prosser. He first wrote Prosser, The Assault upon the Citadel (Strict Liability to the Consumer), 69 Yale L.J. 1099 (1960). Several years later, he finished the story. See Prosser, The Fall of the Citadel (Strict Liability to the Consumer), 50 Minn. L. Rev. 791 (1966) [hereinafter Prosser II].

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completed the demolition[28] and seemed at the time to be the most dramatic aspect of the new rule.

This doctrinal revolution was remarkably swift. What began in 1958 as a modest proposal for strict tort liability for the sale of food "in a condition dangerous to the consumer,"[29] was extended three years later to cover "other products for intimate bodily use" in a "defective condition unreasonably dangerous to the consumer."[30] By 1964, the final form of section 402A applied to "any product."[31] This expansion of the strict liability rule, however, was not accompanied by a thorough analysis of the implications of bringing new classes of products within the sweep of section 402A. As a result, the Restatement does not adequately address the issues raised by generic risks.

A. The Restatement Generally

When the drafters of the Restatement broadened the scope of section 402A to cover all manufactured goods, they apparently assumed that the doctrine and explanatory comments, which had been developed for food and other products "for intimate bodily use," would apply equally well to all manufactured goods. The final version of the section and its comments, therefore, remained virtually intact.[32]

In retrospect, the most significant impact of this rush to strict liability was the confusion and uncertainty that subsequently plagued product-design litigation. Although the concept of design defectiveness was not unknown in 1964,[33] the proponents of section 402A saw no need to adjust the rules to determine explicitly when the new doctrine would impose strict liability for design defects. They retained the terms "defective" and "unreasonably dangerous"[34] and added the requirement that the product "must be dangerous to an extent beyond

[28] Forty-four states have adopted some form of strict liability based upon § 402A. See J. Beasley, Products Liability and the Unreasonably Dangerous Requirement xii-xiii, 97-100 (1981).

[29] Restatement (Second) of Torts § 402A (Tent. Draft No. 6, 1961).

[30] Restatement (Second) of Torts § 402A (Tent. Draft No. 7, 1962).

[31] Restatement (Second) of Torts § 402A (Tent. Draft No. 10, 1964). This version was finally enacted. For other reviews of this evolution, see J. Beasley, supra note 28, at 21-23; Wade, On the Nature of Strict Tort Liability for Products, 44 Miss. L.J. 825, 830-31 (1973).

[32] Compare Restatement (Second) of Torts § 402A comments a-m (Tent. Draft No. 7, 1962) (coverage limited to food and products for intimate bodily use) with Restatement (Second) of Torts § 402A comments a-m (Tent. Draft No. 10, 1964) (coverage extended to all products, with virtually no change in wording of comments).

[33] For an early recognition of this concept, see Noel, Manufacturer's Negligence of Design or Directions for Use of a Product, 71 Yale L.J. 816 (1962).

[34] Restatement (Second) of Torts § 402A (1965).

that which would be contemplated by the ordinary consumer."[35] In subsequent years, courts and commentators alike have found this formulation inadequate and have struggled in vain to fashion an acceptable test for strict liability in product-design cases.[36]

Although the issue of design defectiveness was not recognized as a problem during the evolutionary stages of section 402A, certain other generic risks did occupy the attention of Dean William E. Prosser (the Reporter of the Restatement (Second) of Torts), his advisers (the American Law Institute Council), and the American Law Institute ("ALI") membership. In working out the new rule of strict liability, they were cognizant of the controversy over the causal relationship between cigarette smoking and cancer, as well as of the incidence of serious harm attributed to certain drugs and vaccines,[37] and considered whether the tobacco and pharmaceutical industries should be subject to strict liability.[38] In their floor debates, Dean Prosser and members of the ALI also considered how whiskey would fit into their scheme of liability.[39]

With respect to cigarette-cancer litigation, the Restatement came out unequivocally on the side of the tobacco companies. During a 1961 floor debate on section 402A, a motion was made to delete the word "defective" on the ground that the "unreasonably dangerous" requirement was an adequate test for determining when strict liability should apply and that therefore the term "defective condition" constituted excess baggage.[40] In response to this motion, Dean Prosser pointed out that the ALI Council wanted to retain the element of defectiveness in order to insulate from liability the sellers of dangerous products, such as whiskey, cigarettes, and certain drugs, which are

[35] Restatement (Second) of Torts § 402A comment i (1965).

[36] Citations to the extensive literature and to a sampling of judicial decisions dealing with the test for liability in design-defect cases may be found in Twerski, Seizing the Middle Ground Between Rules and Standards in Design Defect Litigation: Advancing Directed Verdict Practice in the Law of Torts, 57 N.Y.U. L. Rev. 521, 521 n.1 (1982).

[37] These products are mentioned specifically in the Restatement (Second) of Torts § 402A comments i, k (1965). See also text accompanying notes 40-44, 54-61 infra. Indeed, appellate opinions involving these products already had appeared. See, e.g., Pritchard v. Liggett & Myers Tobacco Co., 295 F.2d 292 (3d Cir. 1961) (cigarettes); Gottsdanker v. Cutter Labs., 182 Cal. App. 2d 602, 6 Cal. Rptr. 320 (1960) (polio vaccine).

[38] See text accompanying notes 40-43 infra. When the ALI was making this decision, early drafts of § 402A applied only to food and to products for intimate bodily use. See Restatement (Second) of Torts § 402A (Tent. Draft No. 7, 1962). Although it is impossible to know for certain, the fact that manufactured goods were excluded from the sweep of § 402A may have affected the drafters' thinking about generic hazards.

[39] American Law Institute, 38th Annual Meeting: Proceedings 87-88 (1962) [hereinafter ALI Proceedings].

[40] Id. at 87. The motion was made by Professor Reed Dickerson.

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inherently dangerous even though there is nothing "wrong" with them.[41] The specter of alcoholics bringing a barrage of suits against distillers apparently haunted the drafters of section 402A.[42] After a very brief discussion, the motion was defeated by a voice vote, and the "defective condition" standard remained a part of section 402A.[43]

The notion that section 402A would apply only to defective products—products that have something wrong with them other than their inherent danger—would seem to exclude most generic risks. It is not clear, however, that this interpretation is what the majority of the ALI had in mind. During the 1961 debate, Dean Prosser agreed with other members that the "unreasonably dangerous" standard was sufficient to protect sellers of products such as cigarettes and whiskey.[44] In

[41] Id. at 87-88.

[42] As Dean Prosser noted during the 1961 floor debate, " 'Defective' was put in to head off liability on the part of the seller of whiskey, on the part of the man who consumes it and gets delirium tremens, even though the jury might find that all whiskey is unreasonably dangerous to the consumer." Id. at 88. What the drafters never realized, however, was that the cure, retaining the requirement of a defect, ultimately would prove worse than the disease.

Judge Goodrich, in his concurring opinion in Pritchard v. Liggett & Myers Tobacco Co., 295 F.2d 292, 301 (3d Cir. 1961), was the first to link cigarettes and whiskey. This linkage is more lyric than logical. This imagery suggests a no-liability conclusion in search of a rationale rather than a result dictated either by doctrine or principle. An apparent zeal to exonerate the tobacco industry from strict liability produced the following giddy pronouncement: "Good tobacco is not unreasonably dangerous merely because the effects of smoking may be harmful; but tobacco containing something like marijuana may be unreasonably dangerous." Restatement (Second) of Torts § 402A comment i (1965).

In arguing that the manufacturer of cigarettes that cause cancer should not be liable for breach of implied warranty (absent some representation that the product is harmless), Judge Goodrich invoked the whiskey analogy and noted that "[e]verybody knows that the consumption of intoxicating beverages may cause several different types of physical harm." 295 F.2d at 302. He went on to assert that there would be no liability for over-consumption of whiskey "unless (1) the manufacturer tells the customer the whiskey will not hurt him or (2) the whiskey is adulterated whiskey." Id. The analogy does not really apply. Plaintiffs in cigarette-cancer cases do not seek damages for harm resulting from excessive or abusive smoking but rather from ordinary smoking over a prolonged period of time. This is the very type of consumption sought by the tobacco companies. Sellers of whiskey, on the other hand, do not overtly encourage the type of over-consumption that causes the harm to which Judge Goodrich adverted.

In addition, Judge Goodrich stated that "[i]f the defendant here takes the position that nobody knows whether cigarettes cause cancer or not but at the same time asserts to buyers that . . . cigarettes do not cause cancer, it is in difficulty if a customer shows that the use of these cigarettes caused cancer in him." Id. The problem he never addresses is whether liability should attach when the seller of cigarettes says nothing to the buyer about the risk of cancer, which is unknown to both buyer and seller, and the risk later materializes. Reference to the over-consumption of whiskey obscures rather than informs his analysis.

In 1961 Judge Goodrich was the Executive Director of the ALI and had participated in the Council discussion to which Dean Prosser referred. See text accompanying note 41 supra; Wade, supra note 31, at 830 n.23.

[43] See ALI Proceedings, supra note 39, at 89.

[44] Id. ("I thought 'unreasonably dangerous' . . . carried every meaning that was necessary . . . .").

drafting comment i to section 402A, he pointed out that many products, including food and drugs, involve "some risk of harm, if only from over-consumption," but this risk did not render such products "unreasonably dangerous." Dean Prosser concluded that the proper test was whether the product was "dangerous to an extent beyond that which would be contemplated by the ordinary consumer who purchases it, with the ordinary knowledge common to the community as to its characteristics."[45] Thus defined, the requirement of unreasonable danger would not be met in cases involving whiskey, the hazards of which are known universally, but might be met in cigarette cases, depending upon the court's determination of what the ordinary consumer knew about the risks of smoking at the time of marketing.[46] Toxic risks are not necessarily excluded, therefore, from section 402A.

Another way to approach the scope of section 402A is to ask whether a product with any kind of generic risk, which was found to be unreasonably dangerous, would meet the separate requirement of defectiveness. The comments to section 402A do not answer this question. Comment i presents examples that shed little light upon the problem. The examples contrast generic risks that are not considered unreasonable ("good" whiskey that makes some people drunk, "good" tobacco that causes harm, "good" butter that deposits cholesterol in the blood and leads eventually to heart attacks) with those that do present unreasonable dangers attributable to defects in the same products (whiskey contaminated with a dangerous amount of fusel oil, tobacco with marijuana, butter with poisonous fish oil).[47] The former pose dangers widely known to the ordinary consumer;[48] the latter present clear instances of something "wrong" with the product. Neither group of examples presents a product, not otherwise defective, with such unreasonable risks that strict liability ought to apply.

Comment g, elaborating upon the concept of "defective condition," is similarly unhelpful. It limits strict liability to situations where "the product is, at the time it leaves the seller's hands, in a *condition* not contemplated by the ultimate consumer, which will be unreasonably dangerous to him."[49] The word "condition," like the contami-

[45] Restatement (Second) of Torts § 402A comment i (1965).

[46] Studies linking smoking and cancer began emerging in the 1940's. See Pritchard v. Liggett & Myers Tobacco Co., 295 F.2d 292, 300 (3d Cir. 1961). Modern consumers, therefore, know a great deal more about the risks of smoking than did previous generations. The hazards might well now be considered "universally known."

[47] Restatement (Second) of Torts § 402A comment i (1965).

[48] This conclusion is based, of course, on a factual finding that cigarettes and butter are harmful.

[49] Restatement (Second) of Torts § 402A comment g (1965) (emphasis added).

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nated product examples, seems to suggest that there must be something "wrong" with the product beyond any inherent capacity to cause harm.

Yet Dean Prosser and the ALI did not intend to exclude from section 402A all products creating generic risks. Comment j states that warnings may be required for "poisonous drugs or those unduly dangerous for other reasons"[50] (categories broad enough to embrace medicines triggering deleterious reactions), a proposition compelling the conclusion that the failure to include such warnings might subject the manufacturer to strict liability. While the comment specifies that the absence of directions or warnings may render the product unreasonably dangerous, it does not explain whether unreasonably dangerous also means that the drug is in a "defective condition."[51] Does comment k shed any light on the meaning of "defective"?

B. The Meaning of Comment k

Comment k, dealing with so-called "unavoidably unsafe products," is more expansive than these other comments. It declares that a drug with proper directions and warnings would be neither defective nor unreasonably dangerous,[52] thus suggesting that the same characteristic (mislabeling) that made the drug unreasonably dangerous might also make it defective. This wording blurs the distinction between the two elements, and the requirement of a defect thus becomes superfluous.[53]

The genesis of comment k may help explain this blurring and comment k's other mysteries. Dean Prosser drafted the comment in response to a proposal at the 1961 ALI meeting that prescription drugs

[50] Id. comment j.

[51] Id. In an article written after he drafted this comment, Dean Prosser indicated that a drug marketed without warnings of dangers, which consumers would not already know about, would be regarded as "defective." See Prosser II, supra note 27, at 801.

[52] See Restatement (Second) of Torts § 402A comment k (1965). The text of comment k, which emphasizes the word "unreasonably," is reprinted in note 9 supra.

[53] See Nader & Page, Automobile Design and the Judicial Process, 55 Calif. L. Rev. 645, 649-50 (1967). For judicial recognition of this point, see Ross v. Up Right, Inc., 402 F.2d 943, 947 (5th Cir. 1968) ("When . . . the product is [manufactured] exactly as intended by the manufacturer, to speak in terms of a 'defect' only causes confusion. . . . The key . . . is whether the product is 'unreasonably dangerous.' "); Hamilton v. Motor Coach Indus., 569 S.W.2d 571, 577 (Tex. Civ. App. 1978) ("one who sells a nondefective unreasonably dangerous product without communicating the dangerousness of the product . . . is liable for the injuries inflicted by the unreasonably dangerous item"); Little v. PPG Indus., 92 Wash. 2d 118, 121, 594 P.2d 911, 913 (1979) ("[I]t is inaccurate to speak of a properly manufactured but necessarily dangerous product as being in a 'defective' condition. . . . [I]t is more appropriate to describe an article bearing an inadequate warning as 'unreasonably dangerous' than as 'defective.' ").

be specifically excluded from section 402A.[54] The arguments and the discussion that followed were notably unfocused. The motion under consideration failed to distinguish between harm from adverse reactions and other kinds of drug-induced harm, such as that caused by improper formulation or toxic ingredients.[55] Since no one could argue seriously that the latter risks should escape strict liability, the failure to separate the two categories muddled the debate. Moreover, neither Dean Prosser nor the ALI member who made the proposal indicated how he thought section 402A would apply to prescription drugs in the absence of an explicit exemption. A solution was being offered for a problem that never had been clearly defined. Nor were adverse reactions about which warnings had been issued at the time of marketing distinguished from other harmful effects not discovered until later.

There was also disagreement over the scope of the proposed exemption. The motion proposed to insulate all prescription drugs from strict tort liability.[56] Dean Prosser suggested that a better case could be made for excluding "relatively new, experimental, and uncertain drugs, of which there are a great many on the market, and justifiably so."[57] He defined the term "experimental drug" to include virtually all prescription drugs and even some over-the-counter medicines.[58] Dean Prosser's use of the adjective "experimental" went far beyond clinical testing, an initial stage of the Food and Drug Administration ("FDA") approval process, and covered drugs that had completed the entire approval process and had been marketed to consumers.[59] Thus, he was suggesting an exemption even broader than that proposed by the motion.[60] The motion to include an exemption

[54] See ALI Proceedings, supra note 39, at 90-92. Harold B. Gross of New York City made the motion.

[55] Dean Prosser, criticizing the motion, observed that a pharmacist who supplies poisoned epsom salts clearly should be liable to the injured consumer. Id. at 92.

[56] Id. at 90, 97.

[57] Id. at 93. Dean Prosser's assertion that a great many experimental and uncertain drugs were justifiably on the market, offered ex *cathedra* and without documentation, was a debatable one at best. See generally M. Mintz, The Therapeutic Nightmare (1965); M. Shapo, A Nation of Guinea Pigs: The Unknown Risks of Chemical Technology (1979). If the assertion stands as a basis for comment k, it demonstrates strikingly the weakness of the Restatement drafting process as a mechanism for resolving policy issues.

[58] ALI Proceedings, supra note 39, at 96. Dean Prosser also saw a need to treat "experimental foods" in a similar fashion. Id. at 94. For an argument against exempting new and experimental foods from strict liability, see Comment, Cigarettes and Vaccine: Unforeseeable Risks in Manufacturers' Liability Under Implied Warranty, 63 Colum. L. Rev. 515, 533 (1963).

Clinical testing is a prerequisite for FDA approval of a new drug. For a description of the process by which the FDA approves new drugs, see generally 1 J. O'Reilly, Food and Drug Administration ch. 13 (1982). This approval process helps to insure that information about some risks associated with the approved drugs becomes known after widespread and long-term use.

[59] The only other member to speak on the issue besides Dean Prosser, Donald J. Farage of Philadelphia, opposed any exemption. See ALI Proceedings, supra note 39, at 97.

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for prescription drugs in section 402A ultimately was defeated,[61] as was a subsequent motion to insert such an exception in the comments.[62] On its face, this defeat did not seem to reflect a desire by the membership to exclude *more* than prescription drugs from section 402A, but Dean Prosser apparently saw things differently.

Reflecting the murkiness of its origins, the version of comment k that emerged from the Reporter's hand failed to delineate in any meaningful way either the breadth of its coverage or its purpose. The comment first addresses "unavoidably unsafe products," which it defines as "products which, in the present state of human knowledge, are quite incapable of being made safe for their intended and ordinary use."[63] The comment then appears to focus on "the field of drugs," where such products are "especially common," and presents three overlapping categories of unavoidably unsafe products: high-benefit, high-risk drugs, such as the vaccine used for the treatment of rabies; "many other drugs, vaccines, and the like, many of which [because of high risks involved] cannot legally be sold except to physicians, or under the prescription of a physician;" and "many new or experimental drugs."[64]

The comment furnishes no criteria for determining how risky and how beneficial a drug must be in order to qualify under the first category as "unavoidably unsafe." In any event, such a determination would appear to be unnecessary for drugs. The second category may reasonably be read to include all prescription drugs, since federal law mandates that any medicine with toxic effects that render it unsafe as self-medication be sold under prescription[65]—and a high-risk, high-benefit drug surely would be limited to sale by prescription. The sweeping requirement of prescription status also makes the third category superfluous, a fortunate occurrence since the term "new or experimental drugs" is highly ambiguous.[66]

[61] Id.

[62] Id. at 98.

[63] Restatement (Second) of Torts § 402A comment k (1965). For a detailed analysis of comment k, see Willig, The Comment k Character: A Conceptual Barrier to Strict Liability, 29 Mercer L. Rev. 545 (1978).

[64] Restatement (Second) of Torts § 402A comment k (1965).

[65] See 21 U.S.C. § 353(b)(1)(B) (1976) ("A drug intended for use by man which . . . because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe for use except under the supervision of a practitioner licensed by law to administer such drug . . . shall be dispensed only [upon prescription]. . . .").

[66] The adjective "experimental" seems to refer to the clinical-testing phase of the new-drug approval process. For descriptions of this phase of the process, see 1 J. O'Reilly, supra note 59, at 13-39 to 13-46; Campbell, Civil Liability for Investigational Drugs: Part I, 42 Temple L.Q. 99, 106-07 (1969). While the subsequent reference to the "marketing" of such drugs suggests that they are generally available, the distribution of drugs used in clinical trials actually is highly supervised. Coincidental with the evolution of § 402A and its comments was the passage of the Drug Amendments of 1962, which tightened up new drug clearance procedures. See Drug Industry Act of 1962, Pub. L. No. 87-781, § 104, 76 Stat. 780, 784 (amending 21 U.S.C. §§ 331, 348, 355 (1976)).

Moreover, it is not at all clear what the drafters of § 402A meant by a new but nonexperimental drug. The Food, Drug, and Cosmetic Act defines "new drug" as any drug "not generally recognized . . . as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof . . . ." 21 U.S.C. § 321(p)(1) (1976). Dean Prosser's drug terminology, by drawing this distinction between new and experimental drugs, did not seem to conform to the statutory definition.

[67] Restatement (Second) of Torts § 402A comment k (1965).

[68] See W. Prosser, The Law of Torts 149 (4th ed. 1971) ("It is fundamental that the standard of conduct which is the basis of the law of negligence is determined by balancing the risk, in light of the social value of the interest threatened, and the probability and extent of the harm, against the value of the interest which the actor is seeking to protect, and the expedience of the course pursued.").

Although courts might theoretically find the mere marketing of a dangerous product negligent because the risks outweighed the benefits, they have not yet done so. At least one recent case has asserted this claim against handgun manufacturers. See First Amended Complaint for Damages at 10-11, Brady v. Hinckley, No. 82-0549 (D.D.C. Sept. 8, 1982). See generally Note, Manufacturers' Liability to Victims of Handgun Crime: A Common Law Approach, 51 Fordham L. Rev. 771 (1983); Note, Manufacturers' Strict Liability for Injuries from a Well-Made Handgun, 24 Wm. & Mary L. Rev. 467 (1983). For the argument against using product liability as a means to achieve gun control, see D. Santarelli & N. Calio, Turning the Gun on Tort Law: Aiming at Courts to Take Products Liability to the Limit (1982) (Washington Legal Foundation Monograph).

[69] See text accompanying notes 61-62 supra.

Thus, if its examples are taken seriously, comment k reasonably could be read as excluding from section 402A only unavoidably unsafe prescription drugs. The comment, however, fails to explain what might render an unavoidably unsafe product "defective" and thus subject to section 402A in the first instance. Instead, it states that if the known benefits of one of these products outweigh its known risks, it would not be considered "unreasonably dangerous," provided that it was prepared properly and bore adequate warnings and directions for use.[67] The negative implication of this statement radically expands the scope of the exemption. Since injury caused by any product whose risks outweigh its benefits presumably would be actionable under traditional negligence principles,[68] comment k may be read to remove from the reach of section 402A any product that is unavoidably unsafe as long as the manufacturer will not be subject to liability under a negligence rule for injury caused by the product. Such an exemption includes but is not limited to prescription drugs, an ironic turn in light of the ALI vote rejecting the proposed exemption for prescription drugs alone.[69]

To appreciate the effect of this interpretation of comment k, it is necessary to consider how sellers of unavoidably unsafe products might be held strictly liable in the absence of comment k. The con-

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sumer-contemplation test of comment i[70] seems to preclude liability in cases where the risks generally were known and therefore within the contemplation of the ordinary consumer. Under this test, if a patient suffers harm from a high-risk, high-benefit drug and the harm falls within the scope of the contemplated risk, the drug would not be unreasonably dangerous. Similarly, a warning about an adverse reaction listed on the label of a prescription drug would be considered part of the contemplated risk,[71] as would be true of known risks posed by experimental drugs. Given the broad sweep of comment i, one can salvage independent meaning for comment k only by surmising that, *without* comment k, harm from unknown risks, or harm from known risks which turns out to be much graver than expected, generally would be actionable under theories of strict tort liability. *With* comment k, therefore, one must surmise that a manufacturer of a product posing such risks would escape liability under section 402A if the product were "unavoidably unsafe."

This analysis suggests that the function served by comment k is to exempt unknown risks created by unavoidably unsafe products, since comment i already excludes known risks. Yet this interpretation presents difficulties. The text of comment k is not at all specific on the point, and a matter as important as the treatment of unknown hazards merits direct mention.[72] Moreover, the comment focuses on *known* risks. Two of the three categories listed in the comment involve products unavoidably unsafe because of known risks,[73] such as a rabies

[70] See text accompanying note 45 supra.

[71] In the case of prescription drugs, the manufacturer discloses risks to the prescribing physician. The physician is then under a legal duty to inform patients of material risks associated with drug therapy. See Merrill, supra note 15, at 65-67. In rare instances, courts have imposed a duty upon the manufacturer to insure that the patient is aware of these risks. See, e.g., Reyes v. Wyeth Labs., 498 F.2d 1264, 1276-78 (5th Cir.) (polio vaccine), cert. denied, 419 U.S. 1096 (1974); Davis v. Wyeth Labs., Inc., 399 F.2d 121, 130-31 (9th Cir. 1968) (same). Thus, as a general proposition, contemplation of risk by the prescribing physician usually would satisfy the requirement of comment i.

[72] Shortly after § 402A was published in final form, Dean Prosser wrote a law review article in which he noted that "[t]he conclusion would be clearly indicated that, provided that the product, so far as is known at the time of the sale, is reasonably safe for its intended use, there is no liability for unavoidable dangers – if it were not for the state of confusion surrounding the question of lung cancer from smoking cigarettes." Prosser, Strict Liability to the Consumer in California, 18 Hastings L. J. 9, 26 (1966). He apparently was convinced that strict liability should not extend to unknowable hazards. Why the comments to § 402A did not take a forthright position on the issue is puzzling.

[73] See text accompanying notes 64-67 supra. This emphasis is especially apparent in the case of a high-risk, high-benefit product, such as a cancer cure known to have fatal consequences for a small percentage of users. Dean Prosser mentioned such a hypothetical drug during the ALI floor debate on § 402A. See ALI Proceedings, supra note 39, at 54, 93. In referring to comment k, Dean Prosser stressed that it was designed to protect "the person who is selling a drug which is

vaccine. According to the comment, the manufacturers of these drugs should not be strictly liable for harm from the known risk, a proposition seemingly rendered superfluous by comment i. The third category, "new or experimental drugs," however, does cover products that are unavoidably unsafe because of unknown risks. Indeed, one important purpose of the clinical testing of experimental drugs is to learn more about adverse reactions they might cause. On the other hand, since a patient participating in clinical trials must give an informed consent, which includes an understanding that the harmful effects of the drug are not yet fully known,[74] any adverse reaction the patient suffers may be said to fall within the range of consumer contemplation.[75]

Comment j, unlike comment k, speaks specifically to product risks unknown at the time of marketing; but comment j raises more questions than it answers and sheds little light on the meaning of comment k. In discussing the duty to give warnings and directions for use, Dean Prosser indicated that the sellers of food need not provide warnings about common allergic reactions to their products, since they might reasonably assume that consumers who suffer from the allergy are aware of it.[76] This conclusion is consistent with the consumer-contemplation of unreasonable danger test in comment i: to the ordinary consumer with a common allergy, an allergic reaction would be an expected hazard, and hence not unreasonable. The Reporter went on to state, however, that

> [w]here . . . the product contains an ingredient to which a substantial number of the population are allergic, and the ingredient is one whose danger is not generally known, or if known is one which the consumer would reasonably not expect to find in the product, the seller is required to give a warning against it, if he has knowledge, or by the application of reasonable, developed human skill and foresight should have knowledge, of the presence of the ingredient and the danger. Likewise in the case of poisonous drugs, or those

essarily unsafe, although its utility outweighs the risk." American Law Institute, 41st Annual Meeting, Proceedings 360 (1965). Once again the implication is clear that the risk making the drug necessarily unsafe was known at the time the product was marketed.

[74] See 21 C.F.R. § 50.25(b)(1) (1983) (human subject of clinical trials must be told that "the particular treatment or procedure may involve risks to the subject . . . which are currently unforeseeable").

[75] See Campbell, Civil Liability for Investigational Drugs: Part II, 42 Temple L.Q. 289, 335-[illegible] (1970).

[76] "The seller may reasonably assume that those with common allergies, as for example to [illegible] or strawberries, will be aware of them, and he is not required to warn against them." Restatement (Second) of Torts § 402A comment j (1965).

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unduly dangerous for other reasons, warnings as to use may be required.[77]

This language is unclear on a number of points. Why should the duty to warn unwary allergy victims be limited to cases in which a "substantial" segment of the populace is affected? Under ordinary negligence principles, one might find the risk of serious harm or death to a miniscule percentage of individuals, or even a single individual, to be sufficient justification for requiring a warning.[78] Also, if the risk is undiscoverable in the exercise of due care and hence need not be mentioned in the warnings or instructions for use, does it follow that the manufacturer will not be strictly liable for harm resulting from the risk? This seems to be a fair reading of the text. If so, strict liability will not attach even though the product was dangerous beyond the contemplation of the ordinary consumer.

But what are the reasons for this departure from the comment i test? Does the last sentence of the paragraph indicate merely that drugs fall within the scope of the general duty to give warnings or directions in every case? Or does it mean that allergic reactions to drugs should be governed by the same principles applicable to reactions to food, i.e., that users need not be warned about common risks that are known by both the manufacturer and the consumer? Should it be read even more expansively to preclude liability for harm from all unknowable adverse drug reactions, and, by extension, from all unknowable generic risks? If this gloss on the language of comment j is correct, comment k again would serve no purpose.

Another noteworthy aspect of comment k is its suggestion that strict liability not be imposed on the manufacturers of "new or experimental" drugs containing harmful or impure ingredients that could not be eliminated "because of lack of time and opportunity for sufficient medical experience."[79] The scope of the "unavoidable product danger" exception would be extended beyond generic risks and would apply to garden variety defects, where something is actually "wrong"

[77] Id.

[78] See Wright v. Carter Prods., Inc., 244 F.2d 53, 56 (2d Cir. 1957) (allergic reaction to deodorant; duty to warn even though "only a miniscule percentage of potential customers could be endangered"); Braun v. Roux Distrib. Co., 312 S.W.2d 758, 768 (Mo. 1958) (duty to discover and warn of risks of serious allergic reaction; plaintiff was apparently first to suffer reaction from defendant's hair dye); see also Keeton, Products Liability - Liability Without Fault and the Requirement of a Defect, 41 Tex. L. Rev. 856, 866 (1963). But see Cudmore v. Richardson-Merrell, Inc., 398 S.W.2d 640, 644 (Tex. Civ. App. 1965) (adverse reaction to MER/29; manufacturer liable only if an "appreciable number" of people experience the adverse reaction), cert. denied, 385 U.S. 1003 (1967).

[79] Restatement (Second) of Torts § 402A comment k (1965).

with some units of the product. Such a view reads into comment k an "impure ingredient" exception.[80]

If the risk of an impure or otherwise deleterious ingredient is known when a drug is marketed, but the manufacturer could not discover which doses contained the substance (as is the case of blood contaminated with serum hepatitis), an adequate warning on the label of the drug would place the defect within the scope of consumer expectations. The product thus would not be unreasonably dangerous under the comment i test.[81] Impure ingredients whose presence is not known when the drug is sold (such as the offending agents in the polio vaccine case) pose a more difficult problem because of their similarity to impurities in food and manufacturing defects in mass-produced goods. The seller may be unaware of these defects and may be unable to discover them by economically feasible methods. But these instances are plainly covered by the strict liability rule of section 402A.[82]

The comment k "impure ingredient" exemption should not apply to either of these cases. The exception should be narrowly limited to emergencies in which the usual precautions for assuring the purity of ingredients have not been taken, yet there is medical justification for using the drug.[83] The appropriate scope of the exception is thus so narrow that the exception would make more sense as an interpretation of the consumer contemplation test of comment i than as an exception to the strict liability rule of section 402A: in this particular context, assuming an adequate warning has been given, the risk of harmful ingredients is within the ambit of consumer contemplation.

In conclusion, the Restatement's treatment of generic risks falls short on several counts. The requirement of a "defect" as a distinct element of strict liability was inserted to serve a function already

[80] A California decision might well have inspired this "impure-ingredient" exception. See Gottsdanker v. Cutter Labs., 182 Cal. App. 2d 602, 607-08, 6 Cal. Rptr. 320, 323 (Dist. Ct. App. 1960). In *Gottsdanker*, live polio virus constituted the "impure ingredient" in a polio vaccine. The court applied strict liability under a theory of implied warranty from the producer of the vaccine, since the specifications of the vaccine called for only inactive polio virus.

[81] In at least two blood-contamination cases, the labels on the products bore warnings, but the courts chose to ignore comment i, and instead used comment k as a basis for finding for the defendants. See Brody v. Overlook Hosp., 127 N.J. Super. 331, 339-40, 317 A.2d 392, 397 (App. Div. 1974), aff'd per curiam, 66 N.J. 448, 332 A.2d 596 (1975); Hines v. St. Joseph's Hosp., 86 N.M. 763, 764-65, 527 P.2d 1075, 1076-77 (Ct. App. 1974).

[82] The rule of strict liability applies even though "the seller has exercised all possible care in the preparation and sale of his product." Restatement (Second) of Torts § 402A(2)(a) (1965); see also Wade, Strict Tort Liability of Manufacturers, 19 Sw. L.J. 5, 13 (1965) ("If the article left the defendant's control in a dangerously unsafe condition . . . the defendant is liable whether or not he was at fault in creating that condition or in failing to discover and eliminate it.").

[83] One hypothetical example would be the emergency production of a new vaccine to combat a serious and rapidly spreading epidemic.

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adequately addressed by the "unreasonably dangerous" test. The Restatement fails to make a clear distinction between known and unknown hazards, and never takes a forthright position on which of these two types of hazards strict liability should cover: either, neither, or both. This omission is surprising given the evident concern, reflected both in the ALI floor debates and the comments, over the effect of section 402A upon the manufacturers of drugs, vaccines, and cigarettes. Comment k also is vague in that it fails to make clear what kind of special rule it puts in place, what purposes it meets, and to what classes of products it applies. Finally, the ALI's position on generic product risks, uncertain though it may be, reflects policy judgments. While the ALI is a distinguished body, it is a private, nongovernmental entity.[84] The courts have ultimate responsibility for translating policy into common-law rules, and the matter of liability for generic risks, and for toxic products in particular, requires more comprehensive scrutiny than has been afforded by the Restatement.

III

Generic Product Risks Reconsidered

When the Restatement's commentary on adverse reactions to drugs, food, and tobacco was drafted, the proposed rule of strict liability did not cover all products placed in the stream of commerce.[85] Thus, there was no need to consider how the full range of generic risks should be integrated into the framework of a strict liability system. Even had the drafters reflected on this issue, their efforts may not have produced an internally consistent doctrine to cover harm from the ill effects of products for human consumption and intimate bodily use, and harm from the designed-in dangers of mass-produced goods, for the problem is not an easy one.

There are two basic approaches to the issue of liability for the deleterious effects of generic risks. One approach is to focus on strict liability as it has evolved in design-defect and warning cases, and to ask whether the manufacturer's duty to eliminate[86] or warn of product dangers extends to the particular generic hazard in question. The other approach is to ask whether the policy justifications for imposing

[84] For a description of the process by which the Restatements are drafted, see Goodrich, The Story of the American Law Institute, 1951 Wash. U.L.Q. 283, 287.

[85] See Restatement (Second) of Torts § 402A (Tent. Draft No. 7, 1962); text accompanying notes 29-31 supra. Dean Prosser did not hide his belief, however, that the case law was moving in that direction. See ALI Proceedings, supra note 39, at 52-55.

[86] The manufacturer's duty might also extend to refraining from designing in product dangers.

strict tort liability in cases involving nongeneric risks, i.e., construction defects, where there is general agreement that it should be imposed, support the extension of strict liability to cases involving generic risks. Each of these approaches will be considered in the remainder of this section.

A. *Justifying Strict Liability for Generic Risks: Is the Duty in Design-Defect and Warning Cases Adequate?*

Under well settled principles of negligence law, a manufacturer has a duty to use reasonable care in the design of a product.[87] This obligation requires the manufacturer to use precautionary measures which are economically and technologically feasible,[88] and which will eliminate unreasonable risks of harm. The duty extends to risks of which the manufacturer is aware and, in the exercise of due care, should be aware.[89] If a hazard may be reduced by providing information to the user of a product, the duty of reasonable care may be discharged by providing instructions and warnings.[90]

To have meaning in design cases, the concept of strict liability must make the manufacturer answerable for product-related harm for which negligence theories would provide no remedy. Strict liability potentially might extend to all generic risks, to risks that are designed into a product as well as to those naturally and unavoidably present.[91] The failure to design out or to warn against these risks would render the manufacturer liable, even though the design change or warning might be economically or technologically infeasible, and even though the risk may have been unknown or unknowable at the time of production.

[87] See 1 L. Frumer & M. Friedman, Products Liability § 7 (1982).

[88] The duty of reasonable care has been interpreted, within an economically rational (i.e., profit maximizing) framework, as requiring an actor to expend on accident prevention an amount up to the projected cost of accidents that might occur in the absence of such an outlay. See Posner, A Theory of Negligence, 1 J. Legal Stud. 29, 32-33 (1972). The duty also obliges manufacturers to keep reasonably "abreast of techniques used by practical men in the industry." Noel, Recent Trends in Manufacturers' Negligence As to Design, Instructions or Warnings, 19 Sw. L.J. 43, 51-52 (1965) (citing cases).

[89] For a discussion of the manufacturer's duty to test, see 1 L. Frumer & M. Friedman, supra note 87, § 6.

[90] See id. § 8.

[91] A rule of absolute liability would hold manufacturers responsible for all harm causally related to a product whether or not the product was defective. A rule of liability for harm from all generic risks associated with a product would be somewhat less than absolute, but nonetheless "ultra-strict." For a discussion of absolute liability in the products context, see Schwartz, Foreword: Understanding Products Liability, 67 Calif. L. Rev. 435, 441-48 (1979) (referred to as "extreme strict liability"). For use of the term "ultra-strict liability," see Owen, Rethinking the Policies of Strict Products Liability, 33 Vand. L. Rev. 681, 714 (1980).

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A theory of "ultra-strict" liability for harm from all generic hazards has found neither judicial nor scholarly acceptance. As Professor Gary Schwartz has argued in a similar context, if loss spreading is our goal, we ought not to adopt a rule that discriminates against the victims of nonproduct-related accidents.[92] Courts adopting "ultra-strict" product liability would find themselves on the fabled slippery slope and would be unable to offer any logical reason for not extending the doctrine to other contexts in which the public is routinely exposed to the risk of injury, such as the operation of premises held open for business or public purposes[93] or leased to tenants.[94] Such radical changes in the common law surely and properly would encounter judicial hesitation, grounded upon the conviction that it would be more appropriate to leave the difficult policy judgments involved in adopting such an expansive rule to the legislature.[95]

The rejection of "ultra-strict" liability leaves open, however, the theoretical possibility of imposing strict liability for *some* harm caused by generic risks. For example, suppose an automobile manufacturer is deemed not liable for all harm to occupants who collide with the interior of a vehicle. Is there any way to assign responsibility for some but not all injuries attributable to the generic risks of the so-called "second collision"—to assign responsibility in fewer than all cases, as would be done under a rule of ultra-strict liability, yet in more cases than would be done under a rule of negligence? In other words, are there second collisions that the manufacturer could not have avoided by exercising reasonable care but for which the manufacturer should be held liable? This question has provoked considerable academic debate, much of it sharply critical of courts that have answered "yes" and imposed liability for injuries that were not reasonably avoidable

[92] Schwartz, supra note 91, at 445. Professor Schwartz also points out that the rule might not deter certain kinds of accidents, such as those caused by plaintiffs themselves or by other participants in the event, and that it might be difficult to determine which of several manufacturers whose products were involved in the accident ought to be held liable. Id. at 441-45. It is questionable whether his analysis, focusing on absolute liability, would apply equally in the context of "ultra-strict" liability for harm from generic risks.

[93] See Ursin, Strict Liability for Defective Business Premises: One Step Beyond *Rowland* and *Greenman*, 22 U.C.L.A. L. Rev. 820 (1975) (case for applying strict liability for harm from dangerously defective business premises).

[94] See Love, Landlord's Liability for Defective Premises: Caveat Lessee, Negligence, or Strict Liability?, 1975 Wis. L. Rev. 19, 134-44 (case for applying strict liability for harm from defective leased premises).

[95] See Epstein, Products Liability: The Search for the Middle Ground, 56 N.C.L. Rev. 643, 660-61 (1978) (legislatures are better suited than courts to consider and resolve issues raised by absolute or ultra-strict product liability); Owen, supra note 91, at 705-06 (legislature is more appropriate body to effectuate "distributive justice" via product liability rules).

without articulating a clear, workable standard for deciding when an alleged design flaw is defective or unreasonably dangerous.[96] The emerging consensus seems to be that design defects are best dealt with under a balancing test,[97] which is indistinguishable from the negligence standard. Thus, the failure to develop judicially administrable criteria for strict liability has led to the conclusion that product manufacturers, absent negligence, should not be liable for failing to design out functional dangers. Commentators have concluded, in short, that there is no middle ground between negligence and "ultra-strict" liability, at least in cases involving design defects.

The one exception to this proposition, originally articulated by Deans Page Keeton[98] and John Wade,[99] and since adopted in several

[96] Design liability falling between the poles of ultra-strict liability and negligence may be imposed under the consumer-expectation test, which asks what type of design features guarding against the risk of injury an ordinary consumer would have expected. Another compromise approach would use a fault-based standard which lessens the burdens traditionally assigned to plaintiffs in negligence cases. For a decision permitting both approaches, see Barker v. Lull Eng'g Co., 20 Cal. 3d 413, 132, 573 P.2d 443, 455-56, 143 Cal. Rptr. 225, 237-38 (1978) (plaintiff may use either consumer-contemplation test or negligence-type balancing test, in which the burden is on defendant to establish that the design feature in question was not defective).

For criticisms of *Barker*, see, e.g., Birnbaum, supra note 13, at 602-18; Epstein, supra note 95, at 650-54; Henderson, Renewed Judicial Controversy Over Defective Product Design: Toward the Preservation of an Emerging Consensus, 63 Minn. L. Rev. 773, 782-97 (1979). For an exhaustive and painstakingly fair-minded discussion of *Barker*, see Schwartz, supra note 91, at 464-82.

[97] For a classic balancing test, see Wade, supra note 31, at 837-38 (discussing factors used to weigh the risk of a product against its utility). Such an analysis has been adopted by several courts. See, e.g., Hagans v. Oliver Mach. Co., 576 F.2d 97, 99-100 (5th Cir. 1978); Bowman v. General Motors Corp., 427 F. Supp. 234, 244 (E.D. Pa. 1974). Other scholars have also urged the adoption of balancing tests. See Keeton, Product Liability and the Meaning of Defect, 5 St. Mary's L.J. 30, 37-38 (1973).

For the emerging consensus, see Birnbaum, supra note 13, at 649 (concluding that design defect cases should be decided under a negligence standard); Schwartz, The Uniform Product Liability Act—A Brief Overview, 33 Vand. L. Rev. 579, 584-87 (1980) (discussing adoption of a negligence test for design and warning cases in the Uniform Product Liability Act).

[98] See Keeton, Products Liability—Adequacy of Information, 48 Tex. L. Rev. 398, 407-08 (1970) ("[T]he fact that the maker was excusably unaware of the extent of the danger and had not committed any negligent act or omission that caused the danger would be entirely irrelevant."); Keeton, Some Observations About the Strict Liability of the Maker of Prescription Drugs: The Aftermath of MER/29, 56 Calif. L. Rev. 149, 158 (1968) ("A drug or any other product is unreasonably dangerous, I suggest, if, and only if, a reasonable man, with knowledge of the condition of the product and an appreciation of all the risks as found to exist at the time of the trial, would not now market the product at all or would do so pursuant to a different set of warnings and instructions as to use."). For the earliest mention of this exception, see Keeton, Products Liability—Current Development, 40 Tex. L. Rev. 193, 210 (1961) (concluding that "excusable ignorance of a defect or the properties of a product is immaterial as regards warranty liability").

[99] See Wade, supra note 31, at 834 ("assume that the defendant knew of the dangerous condition of the product and ask whether he was negligent in putting it on the market"); Wade,

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jurisdictions,[100] is that knowledge of risks should be imputed to the manufacturer as of the time of production or sale. Thus, in determining whether to impose liability for failure to design out or warn of a danger, a jury might take into account hazards that were unknown, or even unknowable, to the manufacturer when the product was marketed. That the manufacturer could not have discovered these risks in the exercise of reasonable care would be irrelevant; if a hypothetical reasonable manufacturer, aware of these risks, would not have marketed the product or would have warned of the dangers, an injured plaintiff may recover.[101]

This exception uses hindsight to achieve a genuine strict liability in certain cases of generic risks, such as adverse reactions to drugs, dusts, and chemicals. This hindsight approach, however, has not

supra note 82, at 15 ("[A]ssuming that the defendant had knowledge of the condition of the product, would he then have been acting unreasonably in placing it upon the market?"). Dean Wade has recently stated that he never intended this broad language to apply to unknowable hazards, but only to manufacturing flaws in the condition of the product. See Wade, On the Effect in Product Liability of Knowledge Unavailable Prior to Marketing, 58 N.Y.U. L. Rev. 734, 765 (1983). His position has heretofore widely been interpreted as being identical to that of Dean Keeton. See Birnbaum, supra note 13, at 619; Powers, supra note 13, at 791; Veltri, Products Liability: The Developing Framework for Analysis, 54 Or. L. Rev. 293, 299 (1975). But see Phillips v. Kimwood Mach. Co., 269 Or. 485, 492 n.6, 525 P.2d 1033, 1036 n.6 (1974) (en banc).

[100] See, e.g., Olsen v. Royal Metals Corp., 392 F.2d 116, 119 (5th Cir. 1968); Helene Curtis Indus., Inc. v. Pruitt, 385 F.2d 841, 850 (5th Cir. 1967), cert. denied, 391 U.S. 913 (1968); Dorsey v. Yoder Co., 331 F. Supp. 753, 759-60 (E.D. Pa. 1971), aff'd mem., 474 F.2d 1339 (3d Cir. 1973); Beshada v. Johns-Manville Prod. Corp., 90 N.J. 191, 200, 447 A.2d 539, 544 (1982); Phillips v. Kimwood Mach. Co., 269 Or. 485, 492, 525 P.2d 1033, 1036 (1974) (en banc).

[101] If knowledge or risk as of the time of marketing is to be imputed to the manufacturer, it would seem logical also to impute subsequently acquired knowledge of inefficacy. Hence, factors to be weighed in a strict liability action would include newly discovered information about risks *and* benefits. A New Jersey intermediate appellate court has refused to apply the hindsight approach to either risks or benefits in a DES decision. See Ferrigno v. Eli Lilly & Co., 175 N.J. Super. 551, 576, 420 A.2d 1305, 1318 (Law Div. 1980). The court felt itself bound by comment k in product liability cases and interpreted the comment as mandating a foresight test.

It would also seem logical that, if the product might reasonably have been marketed with knowledge of the risk and with adequate warnings, plaintiffs should have to establish that such warnings would have led them not to use the product. See Henderson, supra note 11, at 946-48. In most cases, however, this requirement would hinge resolution of the causation issue upon plaintiffs' credibility. Alternative approaches have been adopted. See Reyes v. Wyeth Labs., 498 F.2d 1264, 1281 (5th Cir.) (presumption, rebuttable by the manufacturer, that warning would have been heeded), cert. denied, 419 U.S. 1096 (1974); Canterbury v. Spence, 464 F.2d 772, 791 (D.C. Cir. 1972) (causation to be determined by asking what a reasonable person in plaintiff's position would have decided if informed of all risks), cert. denied, 409 U.S. 1064 (1974); Model Uniform Product Liability Act § 104(C)(3) (Dep't of Commerce 1979), 44 Fed. Reg. 62,714, 62,721 (1979) ("claimant must prove by a preponderance of the evidence that if adequate warnings or instructions had been provided, they would have been effective because a reasonably prudent product user would have either declined to use the product or would have used the product in a manner so as to have avoided the harm").

received much policy-oriented justification either by courts or commentators.[102] The mere fact that it created a well-delineated area of strict liability in design and warning cases seemed to suffice. It was inevitable that a need for a firmer rationale would arise.

The recent decision of the New Jersey Supreme Court in *Beshada v. Johns-Manville Products Corp.*[103] attempted to provide such a rationale. The court held that asbestos manufacturers might be liable for lung diseases caused by exposure to asbestos dust at a time when the risks were unknown and undiscoverable, offering three reasons to support this extension of strict tort liability: the allocation of the costs of injuries to the parties best able to bear them; the reduction of risks by increasing incentives for safety research; and the elimination of the need for plaintiffs to prove scientific knowability, a factual determination that is too complex and speculative for jury resolution.[104] The potential problems with each of these reasons will be considered in turn.

The first rationale offered, the notion that manufacturers of defective or unreasonably dangerous products are in a superior posi-

[102] The applicability of the hindsight approach to drugs and cigarettes has been criticized. See, e.g., Connolly, The Liability of a Manufacturer for Unknowable Hazards Inherent in His Product, 32 Ins. Couns. J. 303, 306 (1965); Comment, supra note 58, at 530-35. For an effort to meet some of these criticisms, see James, The Untoward Effects of Cigarettes and Drugs: Some Reflections on Enterprise Liability, 54 Calif. L. Rev. 1550, 1555-58 (1966).

[103] 90 N.J. 191, 447 A.2d 539 (1982).

[104] See id. at 205-08, 447 A.2d at 547-48. The precise issue in *Beshada* was whether the trial judge erred in denying plaintiffs' motion to strike the defendants' assertion that the danger of which they failed to warn was undiscoverable when the products were marketed. The court referred to this assertion as a "state-of-the-art" defense. See id. at 196, 447 A.2d at 542. The term would seem to apply more properly and precisely to considerations of practical feasibility, relating to technology that might have been used to reduce a known risk. See W. Keeton, D. Owen & J. Montgomery, Products Liability and Safety: Cases and Materials 465 (1980); Model Uniform Product Liability Act § 107(D) and commentary (Dep't of Commerce 1979), 44 Fed. Reg. 62,714, 62,728-30 (1979). The term, however, has also been used to encompass both technological feasibility and state of scientific knowledge. See Murray, The State of the Art Defense in Strict Products Liability, 57 Marq. L. Rev. 649, 651-52 (1974); Spradley, Defensive Use of State of the Art Evidence in Strict Products Liability, 67 Minn. L. Rev. 343, 344-47 (1982).

Beshada is the first case in which the New Jersey Supreme Court has applied the hindsight approach to the unknowable adverse effects of a toxic product. Prior decisions had approved the test where plaintiffs sought recovery for harm from machinery which allegedly had been designed defectively or from a flammable liquid chemical. See Freund v. Cellofilm Properties, Inc., 87 N.J. 229, 239-41, 432 A.2d 925, 930-31 (1981) (flammable chemical); Suter v. San Angelo Foundry & Mach. Co., 81 N.J. 150, 171-72, 406 A.2d 140, 150-51 (1979) (same); Cepeda v. Cumberland Eng'g Co., 76 N.J. 152, 163-75, 386 A.2d 816, 821-27 (1978) (defectively designed machine), overruled in part, 81 N.J. 150, 177, 406 A.2d 140, 153 (1979). An intermediate appellate court in New Jersey has refused to apply the *Beshada* rule in a drug case. See Feldman v. Lederle Labs., 189 N.J. Super. 424, 432-33, 460 A.2d 203, 207-08 (App. Div. 1983).

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tion to allocate the costs of product-related injuries, does not really help to answer the question of what makes a product defective or unreasonably dangerous. Nor does it answer the question of which costs should be shifted.[105] Compared with plaintiffs who are injured by products, manufacturers are almost always better able to bear risks by spreading losses through price adjustments and insurance. This rationale would therefore justify imposing liability for harm from risks known as well as unknown, reasonable as well as unreasonable, and ultimately would lead to "ultra-strict" liability. Because it proves too much, this rationale provides only weak justification for a narrower rule of strict liability.

Professor James Henderson has also criticized the risk-spreading rationale on the ground that a hindsight approach would misallocate the costs of liability from products creating risks that were unknown and unknowable at the time of sale. Manufacturers would add this cost to the prices of different, reasonably safe products or to the same products put to different, safe uses. Since the offending products would already have been priced and sold, their liability costs could not be assigned to them. Moreover, once manufacturers discover the danger, the product is removed from the market or redesigned, or appropriate warnings are given, and thus there is no longer any need to assign costs of liability.[106]

Such a result—product prices reflecting costs other than those caused by the product itself—would lead to market distortions and destroy the optimality properties that flow from cost-based pricing in a perfectly competitive market.[107] In a perfectly competitive market, cost minimization and profit maximization for a particular product, and not costs from earlier versions of a particular product, or different products altogether, will determine the price of the product. A manufacturer who tries to pass on these costs will be driven from the market by manufacturers who do not. Professor Henderson's argument thus squarely poses a paradox: the market distorting effects of misallocation can occur only in a noncompetitive market, where the effects of misallocation are ambiguous.[108] Because of competitive market pressures,[109] unanticipated liability costs are more likely to be paid out of profits, loans, or sources other than price increases.[110]

[105] See Owen, supra note 91, at 703-07.

[106] See Henderson, supra note 11, at 942-44.

[107] A perfectly competitive economy is "efficient" (i.e., scarce resources are allocated optimally) and "Pareto optimal" (i.e., no one can be made "better off" without making someone "worse off"). For a serious yet nonmathematical discussion of these concepts, see J. Quirk, Intermediate Microeconomics 229-45 (1976).

[108] The distortions that make a market noncompetitive also destroy the optimality properties of perfectly competitive equilibrium. Adding additional distortions to the market may improve the situation, or it may make the situation worse. Economists have labelled this ambiguity the theory of the "second best." For a general discussion of this theory, see id. at 243-44.

It is important to distinguish between the allocation that would result from the retroactive application of a hindsight rule and that from the prospective application.[111] The court in *Beshada* pointed out that application of the rule of strict liability for unknowable risks "will force the price of any particular product to reflect the cost of insuring against the possibility that the product will turn out to be defective."[112] Thus, the threat of prospective liability would force a proper allocation of product prices.[113] When a court initially adopts a hindsight rule and imposes it retroactively, however, the prices of products marketed years, or, in the case of asbestos, decades, earlier will not bear their own liability costs.[114] In the case of asbestos, this "first shot" problem is enormous. The New Jersey Supreme Court did not ask whether considerations of fairness deriving from justifiable reliance by asbestos manufacturers,[115] or the enormous potential liability to which the industry might be exposed, supported the recognition of a hindsight rule that would operate prospectively only.[116]

For all of these reasons—because it proves too much, because it may or may not apply depending on market conditions, and because its effectiveness depends on whether the application is prospective or retroactive—the risk-spreading rationale raises more questions than it answers and provides only weak support for a rule of strict liability.

[109] Whether a particular market is competitive, of course, is an empirical question, and the answer can vary from market to market.

[110] If the market is competitive, manufacturers are earning what economists call "normal profits," the profits necessary to continue functioning as an ongoing business. If profits drop, the manufacturer will encounter problems raising new capital (a result of insufficient returns on the capital already invested in the firm) and may have to withdraw from the market. Recovering liability costs from profits, therefore, may drive firms from the market. In noncompetitive markets, however, where firms earn "super profits," the result may be entirely different.

[111] The problem is discussed in Schwartz, New Products, Old Products, Evolving Law, Retroactive Law, 58 N.Y.U. L. Rev. 796, 825 (1983).

[112] 90 N.J. at 206, 447 A.2d at 547.

[113] This conclusion assumes that a manufacturer will be able to obtain adequate protection against the unknown and the unknowable, risks that would have to be translated somehow into monetary terms and factored into the cost of liability insurance premiums, which product prices would then reflect.

[114] Of course, the same is true whenever liability is expanded at common law—parties who have already avoided liability in the past continue to do so under the new rule as well. See R. Keeton, Venturing to Do Justice: Reforming Private Law 25-26 (1969).

[115] Since the hindsight approach was first suggested in 1961, see note 98 supra, manufacturers were arguably on notice that liability for harm from unknowable risks might one day be imposed upon them. In *Beshada*, however, the exposures to asbestos dust dated back to the 1930's.

[116] It would be difficult to apply the hindsight rule prospectively only. If it were limited to injury sustained in the future, or after 1961, problems of proof would greatly complicate cases involving prolonged harmful exposures.

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The second policy justification offered in *Beshada* was that a rule of strict liability would spur safety research that might reveal hidden dangers.[117] Put another way, a contrary rule would benefit producers who were unaware of risks and thus would tend to perpetuate ignorance, especially if plaintiffs could not easily establish that a hazard might have been detected in the exercise of due care. Admittedly, if the existence of a hazard were completely unknown at the time of marketing, a manufacturer would be unable to determine how much to spend in order to make the discovery, and there may be no increase in safety research.[118] On the other hand, if a hazard were suspected or were known to exist but its full extent were not known, the incentive for additional investigation could produce some incremental level of safety. In either instance, though, this incentive for safety research would justify a rule of strict liability because the manufacturer can always uncover the known risks better and more cheaply than the potential victim.[119]

It is worth noting that *Beshada* involved asbestos rather than a drug. Federal regulation prescribes the nature and amount of safety testing that must be done before the marketing of a new medication.[120] In using stimulation of safety research as a rationale for a rule of strict liability for unknown risks, a court would be explicitly or implicitly recognizing a general need for more extensive premarket investigation than presently required by the FDA. This recognition, however, goes far beyond judicial determinations in individual cases that FDA approval of a particular new drug does not preclude a finding of negligence or strict liability.[121] While the safety-incentive

[117] "The 'state-of-the-art' at a given time is partly determined by how much industry invests in safety research. By imposing on manufacturers the costs of failure to discover hazards, we create an incentive for them to invest more actively in safety research." 90 N.J. at 207, 447 A.2d at 548.

[118] It has been argued that the hindsight approach will deter manufacturers from testing to discover whether products already on the market are causing harm. See Henderson, supra note 11, at 940-41. This course of action will be effective only if the harm or its connection with the manufacturer's product remains undetected indefinitely. There are, however, many other ways in which such information may come to light. See, e.g., 15 U.S.C. § 2064(b) (1976) (manufacturers of consumer products required to notify Consumer Product Safety Commission of substantial product hazards); 15 U.S.C. § 1411 (1976) (notification requirement for defective automobiles). Manufacturers would therefore benefit from rapid discovery of harm caused by their products: they can undertake a recall or reduce the risks to reasonable proportions by issuing appropriate warnings.

[119] See notes 132-33 infra.

[120] See 21 C.F.R. §§ 310, 312, 314 (1983) (FDA regulations governing the approval process for new drugs).

[121] For cases finding that FDA approval of a warning is not conclusive on the issue of the adequacy of the warning, see, e.g., Brochu v. Ortho Pharmaceutical Corp., 642 F.2d 652, 658 (1st Cir. 1981); Stevens v. Parke Davis & Co., 9 Cal. 3d 51, 65-66, 507 P.2d 653, 661-62, 107 Cal. Rptr. 45, 53-54 (1973); McEwen v. Ortho Pharmaceutical Corp., 270 Or. 375, 396-400, 528 P.2d 522, 533-35 (1974).

rationale is not indefensible,[122] some courts might give it less weight than they would otherwise because of its far-reaching implications.

Another problem with the accident-avoidance rationale is that it leaves open the following question: why should courts impose strict liability upon manufacturers for harm from hazards of unknown scope as an incentive to discover the true scope of the risks, but not apply strict liability as a spur to technological development where at the time of production it was technologically infeasible to eliminate or to reduce risks? There is widespread agreement that in the latter cases, involving the so-called "state of the art" issue,[123] manufacturers will not be liable, absent negligence, for having failed to use today's safety technology yesterday.[124] It is difficult to distinguish between technology that can detect the gravity of risk and technology that can eliminate or reduce risk, or to conclude that strict liability would act as a spur to the advancement of the former but not of the latter.[125]

The third justification for strict liability offered by the *Beshada* court is that the litigation process cannot adequately determine scientific knowability.[126] But although the same might be said of the need to decide whether a manufacturer failed to exercise reasonable care in designing a product,[127] courts have not stopped resolving these is-

[122] Proposed FDA regulations would streamline the drug-approval process and hence reduce the time required to bring new medications into unrestricted commercial use. See New Drug and Antibiotic Regulation, 47 Fed. Reg. 46,622 (to be codified at 21 C.F.R. pts. 310, 312, 314, 430, 431, 433) (proposed June 23, 1982). The recent removal of the antiarthritic drug Oraflex from the market because of its association with the deaths of a number of users, see Newsweek, Aug. 16, 1982, at 59, col. 1, however, has provoked criticism about the adverse implications for safety of drug deregulation. See N.Y. Times, Aug. 15, 1982, at 7F, col. 2. That the new proposal would permit the FDA to rely more heavily upon foreign clinical studies also has been seriously questioned. See The New Drug Review Process: Hearings on the Regulation of New Drugs by the Food and Drug Administration Before the Subcomm. on Intergovernmental Relations and Human Resources of the House Comm. on Government Operations, 97th Cong., 2d Sess. 312-52 (1982).

[123] The term is used here to mean technological feasibility. See note 101 supra.

[124] See, e.g., Wilson v. Piper Aircraft Corp., 282 Or. 61, 67-69, 577 P.2d 1322, 1326-27 (1978); Boatland of Houston, Inc. v. Bailey, 609 S.W.2d 743, 746, 748 (Tex. 1980).

[125] Professor Henderson, who disapproves of the hindsight rule, argues that strict liability would not provide increased incentives for manufacturers to develop technology that eliminates or lessens risks; the incentive already exists in the market. Even Henderson recognizes, however, that although information about product risks does not generate profits, the subsequently developed risk-reduction technology might well provide competitive advantages to its creator, and a strict liability rule might well stimulate this type of technology. See Henderson, supra note 11, at 952-53. Moreover, risk information may have considerable value in discrediting a competitor's product. See Page, Not So Sure: The Underarm Menace, The New Republic, Apr. 12, 1975, at 8 (competitor discovered hazards associated with a rival's antiperspirant and submitted the data to the FDA).

[126] 90 N.J. at 206-07, 447 A.2d at 548-49.

[127] See Henderson, Judicial Review of Manufacturers' Conscious Design Choices: The Limits of Adjudication, 73 Colum. L. Rev. 1531 (1973) (developing the idea of "polycentricity" — that

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sues.[128] The scientific speculation inherent in deciding whether a particular hazard was knowable may produce more uncertainty than a dispute about whether designing out a known danger was feasible; this greater degree of uncertainty might tip the balance in favor of giving at least some weight to this particular rationale for strict liability. The elimination of the need to establish knowability would certainly reduce trial costs, but so would dispensing with the burden of proving lack of due care in design cases.

Since design and warning cases generally are decided by balancing factors that are virtually identical to those used to determine negligence, it is difficult to justify treating unknown or unknowable generic risks as falling within the duty to design or warn but outside the balancing approach. Ultimately, however, a de facto negligence test for all generic risks is unsatisfactory because this standard does not take into account the compelling policy reasons for adopting a strict liability theory. I now turn to those policy reasons, which have been recognized in the context of nongeneric risks.[129]

B. Justifying Strict Liability for Generic Risks: Are the Policies Underlying Strict Liability in Construction Defect Cases Adequate?

The conceptual treatment of liability for harm from unknowable generic risks as deriving from the manufacturer's duty to design or to warn creates a discomforting impression: that liability is being imposed for a failure to do the impossible. An alternative approach is to view generic risk through the same lens that, when focused upon the risk of harm from construction defects, has produced a rule of strict liability even when it might have been economically infeasible or technologically impossible to eliminate the hazard. Here the theory

design decisions are multifaceted and altering one aspect of a design might cause a "defect" in another part of the design); R. Epstein, Modern Product Liability Law 84-90 (1980) (agreeing with Professor Henderson). For judicial concurrence with this view, see Dawson v. Chrysler Corp., 630 F.2d 950, 962-63 (3d Cir. 1980) (recognizing in dictum that design decisions are polycentric), cert. denied, 450 U.S. 959 (1981).

[128] For explicit rejections of this criticism in the product design context, see Bowman v. General Motors Corp., 427 F. Supp. 234, 242, 245-46 (E.D. Pa. 1977); Owens v. Allis-Chalmers Corp., 326 N.W.2d 372, 377-78 (Mich. 1982); McMullen v. Volkswagen of Am., 274 Or. 83, 86-90, 545 P.2d 117, 119-21 (1976); Schwartz, supra note 91, at 449-51.

[129] The criticism that these same policy reasons might support extensions of the strict liability doctrine beyond product liability does not necessarily preclude modest steps in that direction. Courts traditionally have permitted the common law to develop gradually and incrementally; indeed, case-by-case law making permits no other method. The central role of consumerism in contemporary Western society makes especially appropriate the use of product liability as a testing ground for deviations from traditional fault principles and toward risk spreading.

does not rest so much on any real or presumed inadequacy in the manufacturing process as on a policy decision to impose liability without fault. Thus, it may be appropriate to inquire whether the bases of strict liability for construction defects support a similar rule for generic risks.

Manufacturers are strictly liable for harm from construction defects even if they could not have eliminated, or discovered, such defects by exercising reasonable care.[130] Held to the standard of their own plans and specifications, manufacturers must answer for imperfections that arise from their production processes.[131] Of the various reasons that have been advanced to justify this rule of strict liability in construction defect cases,[132] three seem worthy of discussion in the context of generic risks: accident avoidance, loss spreading, and the satisfaction of justifiable consumer expectations.[133]

[130] See Restatement (Second) of Torts § 402A(2)(a) (1965).

[131] See R. Epstein, supra note 127, at 68. As Epstein notes, this obligation is well settled.

[132] Professors John E. Montgomery and David G. Owen have identified seven policy justifications for imposing strict tort liability on manufacturers of defective products:

> (1) Manufacturers convey to the public a general sense of product quality through the use of mass advertising and merchandising practices, causing consumers to rely for their protection upon the skill and expertise of the manufacturing community.
>
> (2) Consumers no longer have the ability to protect themselves adequately from defective products due to the vast number and complexity of products which must be "consumed" in order to function in modern society.
>
> (3) Sellers are often in a better position than consumers to identify the potential product risks, to determine the acceptable levels of such risks, and to confine the risks within those levels.
>
> (4) A majority of product accidents not caused by product abuse are probably attributable to the negligent acts or omissions of manufacturers at some stage of the manufacturing or marketing process, yet the difficulties of discovering and proving this negligence are often practicably insurmountable.
>
> (5) Negligence liability is generally insufficient to induce manufacturers to market adequately safe products.
>
> (6) Sellers almost invariably are in a better position than consumers to absorb or spread the costs of product accidents.
>
> (7) The costs of injuries flowing from typical risks inherent in products can fairly be put upon the enterprises marketing the products as a cost of their doing business, thus assuring that these enterprises will fully "pay their way" in the society from which they derive their profits.

Montgomery & Owen, Reflections on the Theory and Administration of Strict Tort Liability for Defective Products, 27 S.C.L. Rev. 803, 809-10 (1976). Although these policy justifications apply generally to product liability law, they are particularly relevant to construction-defect cases, where there is general agreement that strict liability should apply.

[133] Judge Traynor advanced these arguments in his seminal concurring opinion in Escola v. Coca Cola Bottling Co., 24 Cal. 2d 453, 461-63, 150 P.2d 436, 440-41 (1944), to support a rule of "absolute liability" for product defects.

> The need to protect consumers from the complexities of modern product technology, the manufacturer's superior capacity to control risks, and the desirability of forcing manufacturers to internalize costs associated with product risks all justify the public policy objective of accident

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Whether strict liability will actually foster accident avoidance has been seriously questioned. It has been argued that producers will avoid only those accidents worth avoiding—if it is cheaper to let an accident happen and to pay the resulting liability costs, the profit-maximizing manufacturer will follow that course. Thus, if testing and quality-control procedures would cost more than projected liability costs, a rule of strict liability would not encourage manufacturers to adopt procedures to prevent accidents.[134]

This argument, however, is not entirely persuasive. A manufacturer bound by negligence principles might foresee escaping some liability costs that should attach when it does not exercise due care. The difficulties of proving fault might be too great for injured plaintiffs in certain kinds of cases,[135] or economic constraints might force plaintiffs to accept unfavorable settlements.[136] Anticipating these lower liability costs, manufacturers might spend less on accident prevention. By reducing plaintiffs' burdens, a strict liability rule might well encourage manufacturers to increase safety expenditures to the level they might reach under a negligence system that functioned optimally.[137]

The adoption of a rule of strict liability in cases where a manufacturer knew a risk existed but did not know its full extent also might increase safety by providing an incentive to perform additional investigations.[138] Indeed, assuming that manufacturers foresee that, under negligence principles, not every injured plaintiff will recover full damages for harm from a particular design feature or warning, the application of strict liability to all generic hazards, known and unknown, will increase the prospect of full recovery, encouraging safety

avoidance. Liberalized discovery procedures and doctrines such as res ipsa loquitur appear sufficient to overcome barriers that might once have been insurmountable to many plaintiffs suffering product related harm.

[134] See Posner, Strict Liability: A Comment, 2 J. Legal Stud. 205, 209 (1973); Sachs, Negligence or Strict Product Liability: Is There Really a Difference in Law or Economics?, 8 Ga. J. Int'l & Comp. L. 259, 274-76 (1978).

[135] Indeed, Judge Traynor relied in part on this rationale in his concurrence in *Escola*. See 24 Cal. 2d at 463, 150 P.2d at 441.

[136] Product liability suits usually are financed through contingent fees. To the extent attorneys perceive "tougher odds" under a negligence regime, they will be less willing to take on cases than they would be under a rule of strict liability. Plaintiffs will thus be unable to "finance" their litigation. Moreover, some plaintiffs may need the money now, even if it is less than they might receive later.

[137] This criticism uses economic theory to respond to an economic argument. In the presence of market imperfections like problems of proof (imperfect information) and costs of litigation (capital market imperfections), there may well be a role for intervention (a rule of strict liability) in the market.

[138] See text accompanying note 118 supra.

expenditures and accident avoidance. This increase in safety enhancement standing alone, however, is probably insufficient to justify liability without fault in these cases.

The "loss-spreading" rationale rests on the manufacturers' ability to use insurance to spread the costs[139] of harm caused by construction defects more efficiently and more easily than product victims can.[140] Construction defects are easily insurable for two reasons: the number of claims likely to arise from such defects is fairly predictable, and this number is likely to be relatively small in comparison with the total number of products placed into the market.[141] Insurance against these risks, therefore, is readily available because the costs are predictable and the harm to be insured against normally will remain within modest bounds.[142] The number of known generic risks likely to occur—ranging from adverse drug reactions for which warnings have been given[143] to automobile accidents[144]—can also be predicted with some certainty. Rough estimates can even be made about risks whose presence is known but whose extent cannot be calculated. The only type of hazard that would not permit even a guess would be the unknown and undiscoverable danger.

In the case of generic risks, however, the other aspect of insurability—a comparatively small number of risks—is absent. Unlike construction defects that affect only a small percentage of users, every generic risk will endanger every user of the product. Thus, the amount of damage attributable to generic product risks could be enormous, even if recoveries are reduced to take into account the

As noted earlier, this rationale leaves open the question of which costs ought to be shifted. See text accompanying note 105 supra.

[140] When dealing with both the manufacturers' and consumers' abilities to insure, I assume the existence of well-functioning insurance markets to which the respective parties have access. Depending on the type of loss one seeks insurance against, this may or may not be an empirically verifiable assumption.

[141] See Owen, supra note 91, at 691-92; Schwartz, supra note 97, at 585. Professor Owen, while acknowledging the predictability of construction defects ("product flaws"), does not view such predictability as a valid basis for distinguishing construction defects from design defects.

[142] Some construction defects, however, have significant costs. For example, construction defects in automobiles may affect large numbers of vehicles. See, e.g., Brown, Rear-Wheel Loss Forces Recall of Millions of GM's Sedans, Wash. Post, Apr. 2, 1983, at C7, col. 5 (improperly manufactured component associated with partial or total separation of rear axle shaft and wheel possible). A defect affecting every automobile could have even more disastrous consequences. See Werber, Automobile Recall Campaigns: Proposals for Legislative and Judicial Responses, 56 Ind. L.J. Urb. L. 1083, 1085 (1979).

[143] The FDA approves new drugs on the basis of cost-benefit judgments that take into account risks of adverse reactions. See 1 J. O'Reilly, supra note 59, § 14.05.

[144] See Owen, supra note 91, at 692 (discussing cost-benefit assessments of fuel tanks in the case of Pintos).

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comparative responsibilities of plaintiffs, third persons, and other enterprises that might appropriately share the losses. One might argue, then, that loss spreading makes sense only in the context of construction defects, where the relatively modest costs can be more easily absorbed by the manufacturer.

An intermediate position might hold manufacturers strictly liable for unavoidable hazards, such as adverse reactions to toxic products, but not for designed-in, functional dangers, such as the speed of an automobile. This compromise position, however, has several problems. As a practical matter, it is difficult to base a rule of strict liability on degrees of potential damage: the notion that the more harm a defendant may cause the less likely it is that liability will attach strikes a somewhat perverse chord. Moreover, the focus on the quantity of loss may well be misguided. If the purpose of loss spreading is to deflect the economic impact of product-related harm away from those who may not be able to absorb it, perhaps the focus should be on the victims' capacity to pay for their own injuries, and not on the aggregate cost of all such injuries.

Consumers' ability to foresee product risks is relevant to a determination of their ability to insure themselves against those risks, and thus to a determination of their capacity to absorb the cost of their own injuries. The policy of satisfying justifiable consumer expectations[145] may shed light on this issue of cost absorption in particular and on the appropriateness of strict liability for generic product risks in general.

The notion that manufacturers should be strictly liable for harm from product frustration is rooted in the doctrine of implied warranty of merchantability, which holds goods to the standard of reasonable fitness for their intended use.[146] Products placed into the stream of commerce carry with them a representation of safety, the scope of which is determined by what the ordinary consumer would expect of those products.[147] This representation of safety underlies the consumer contemplation test set out in comment i of the Restatement.

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[144] For articulations of the consumer-contemplation approach to strict product liability, see generally Hubbard, Reasonable Human Expectations: A Normative Model for Imposing Strict Liability for Defective Products, 29 Mercer L. Rev. 465 (1978); Shapo, A Representational Theory of Consumer Protection: Doctrine, Function and Legal Liability for Product Disappointment, 60 Va. L. Rev. 1109 (1974).

[145] U.C.C. § 2-314 (1978).

[146] See Fischer, Products Liability—The Meaning of Defect, 39 Mo. L. Rev. 339, 348-52 (1974).

It is important to distinguish between two uses of consumer expectations: the goal of meeting justifiable consumer expectations as a policy behind strict tort liability, and the use of consumer expectations as a criterion for deciding whether strict liability should apply in a particular instance. The former derives from the conviction that, as a matter of fairness, consumers should be entitled to rely on the representation of safety made by the seller of a product and by any information accompanying the product. Consumers depend on the manufacturer to provide goods that will meet these implied representations so that they can make rational judgments affecting their own well-being. The imposition of strict liability will encourage producers to satisfy these consumer expectations, will permit consumers to act on the assumption that expectations will be met, and will enable consumers to survive the economic hardship of unexpected losses.[148]

When using consumer expectations as a criterion for applying strict liability, the critical task is to determine which consumer expectations are justifiable. The rule in construction defect cases suggests that courts have found such defects to lie outside the ambit of consumer contemplation; consumers, therefore, may justifiably expect products to be free of construction flaws, and manufacturers will be held strictly liable for all such flaws: known, unknown, and unknowable.[149] In design defect cases, however, courts apply what amounts to a negligence test[150] and say in effect that consumers justifiably may expect only that due care, measured as of the time of manufacture, will be exercised with regard to design and warning decisions.

Is this distinction tenable? Given what the average person undoubtedly knows about product quality (especially in light of the publicity given to recalls of automobiles and other household products), all types of risk-creating flaws, both in construction and design, are arguably within the contemplation of ordinary consumers.[151] In some cases, awareness of a vague possibility that some defect might

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[148] See Shapo, supra note 145, at 1124-31. When consumers expect a loss, they can insure against the loss themselves. It is only when the loss is unexpected that compensation, under a rule of strict liability, is needed.

[149] See text accompanying notes 130-33 supra.

[150] See note 97 and accompanying text supra.

[151] As Professor Owen has argued,

> [F]rom a more abstract perspective of social psychology, it may well be that the typical consumer knows full well that of the thousands of cars spewed out by Detroit on a daily basis many hundred at least will house production errors of various types and levels of danger . . . . It thus may be that consumer expectations are no more violated in cases of production flaws than in those involving design adequacies.

Owen, supra note 91, at 693.

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lurk somewhere within a product ought not to establish the risk as within the consumers' contemplation. The wide range of potential flaws, especially in complex items such as automobiles and workplace machinery, and the varying degrees of potential risk associated with such flaws, renders a general awareness practically useless to the consumer.[152] Moreover, the marketing image of a product may dim an already faint awareness of the risk. A rule of strict liability for construction defects, then, reflects a justifiable judicial determination that consumers merit protection under a standard requiring goods to be completely free of such defects.

A practical reason for limiting justifiable consumer expectations to the exercise of reasonable care in the design of products is that there is no other workable standard by which courts may determine whether a product is unreasonably dangerous. Consumers usually are unable to form an expectation about the extent to which design defects will be eliminated: it is not a matter of expecting one unit of a particular product to be as good as the next.[153] Therefore, the best that consumers can justifiably expect in the design defect context is that manufacturers will use technologically and economically feasible methods to reduce or eliminate foreseeable risks.

The policy of satisfying justifiable consumer expectations also dictates the refusal to impose strict liability for harm from known generic risks. The ordinary consumer appreciates the dangers posed by a speeding automobile or a sharp knife, and would therefore have no cause to believe that a manufacturer would do more than use due care to reduce these hazards. Contemporary smokers know of the risk of cancer from cigarettes. The presence of warnings on the label of prescription drugs makes physicians, acting on their patients' behalves, aware of the relevant risks. In each of these cases, consumers can make a rational judgment about the scope of the hazard and act accordingly.[154]

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[152] See Dickerson, Products Liability: How Good Does a Product Have to Be?, 42 Ind. L.J. 301, 315-16 (1967).

[153] For criticisms of the consumer contemplation test in the design defect context, see Keeton, Products Liability—Design Hazards and the Meaning of Defect, 10 Cum. L. Rev. 293, 300-05 (1979); Montgomery & Owen, supra note 132, at 823; Schwartz, supra note 91, at 471-81.

[154] Dean Keeton has argued that the consumer-contemplation approach to strict liability would deny recovery to plaintiffs injured by an open and obvious design defect. See Keeton, supra note 153, at 302. The so-called "patent danger" rule, developed under negligence law, has been severely criticized. See generally Marschall, An Obvious Wrong Does Not Make a Right: Manufacturers' Liability for Patently Dangerous Products, 48 N.Y.U. L. Rev. 1065 (1973). The recent trend has been to reject the rule and to permit obviousness of risk to be weighed as merely one factor in determining whether a product is unreasonably dangerous. See Pike v. Frank G. Hough Co., 2 Cal. 3d 465, 473-74, 467 P.2d 229, 234-35, 85 Cal. Rptr. 629, 634-35 (1970); Micallef v. Miehle Co., 39 N.Y.2d 376, 384-85, 348 N.E.2d 571, 576-77, 384 N.Y.S.2d 115, 120-21 (1976). See generally Phillips, Products Liability: Obviousness of Danger Revisited, 15 Ind. L. Rev. 797 (1982). Hence, where product risks are open and obvious, plaintiffs may still be able to establish negligent design.

[155] Note that this consumer-expectations rationale, unlike the safety enhancement and loss-spreading rationales discussed above, applies to risks unknown or even unknowable; the focus is on the consumer's state of knowledge, and not on the manufacturer's state of technology.

[156] See Schwartz, supra note 91, at 474-75.

[157] U.C.C. § 2-318 (1978) (alternatives B and C).

[158] Under a negligence test, the manufacturer's duty would be to avoid creating unreasonable risks of harm to foreseeable victims, a class that would include bystanders as well as users. See 1 L. Frumer & M. Friedman, supra note 87, § 5.03(1)(c).

But if the danger or its full dimensions do not become evident until after the plaintiff has been exposed to the product, the consumer-contemplation policy supports the imposition of strict liability. The product has inflicted an unpleasant surprise. Although the manufacturer could not have discovered the danger or its extent, the marketing of the product misled the consumer with an implied representation of safety that was not met and thus deprived the consumer of the opportunity to evaluate the risk and to decide whether to accept it.[155] Under this new view of consumer expectations, a product posing an unknown or unknowable generic hazard would stand on the same footing as a product with a construction flaw: each product would be considered unreasonably dangerous for purposes of strict liability because it frustrated justifiable consumer expectations recognized by the law.

The need to integrate liability for product-related harm to nonconsumers into a scheme structured around consumer expectations raises a conceptual problem. Professor Gary Schwartz has noted that a third-party beneficiary theory can preserve the viability of the consumer-expectations test in instances where the consumer could reasonably be deemed to have contemplated the conferral of accident-avoidance benefits upon others.[156] The extension of the implied warranty of merchantability, which under the Uniform Commercial Code protects anyone "who may reasonably be expected to use, consume or be affected by the goods,"[157] lends support to this argument by analogy. But it would be stretching things beyond the breaking point to assume that a consumer intends to protect bystanders, especially those who are total strangers. As a practical matter, this problem will be limited to construction defect cases: the de facto negligence test used to determine liability in design defect cases applies equally well to consumers and bystanders;[158] and unknown generic risks will rarely endanger

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anyone other than a product user.[159] These limitations, however, do not eliminate the theoretical hurdle.

One answer is simply to recognize that the policy of satisfying justifiable expectations supports the imposition of strict liability only on behalf of consumers and their intended beneficiaries. To hold manufacturers liable without fault for harm to bystanders would then require a separate, independent rationale. A second, and perhaps preferable, solution lies in a reassessment of the consumer-contemplation policy. Its roots, as has been noted,[160] go back to the doctrine of implied warranty of merchantability, the primary concern of which was the adjustment of the rights of parties to commercial transactions. Although courts fashioning tort doctrine may legitimately borrow from sales law, they need not feel fettered by sales law constraints. Where the same policy goals would be applicable to nonconsumers, it might be logical to extend strict liability protection beyond the purchaser. Thus, the user of a product personally relies upon the implied representations of safety inherent in the product. Certain bystanders may also entertain similar expectations that a product will not injure them. This approach would require courts to differentiate between two classes of bystanders: the first is exemplified by a pedestrian injured when an automobile goes out of control because of a construction defect; the second by the person harmed while asleep at home by an airplane that crashed because of a flaw in its assembly. In the latter case, the victim had no expectation generated or frustrated by the product.[161] The falling airplane was like a falling meteorite—completely unexpected—an event for which there is no tort remedy. Hence the consumer-contemplation rationale, expanded to take into account the actual expectations of users and bystanders, would not support recovery by such victims under strict liability.

Conclusion

This Article has proposed a conceptual framework for determining when to apply strict liability to generic product risks. On the twentieth anniversary of the first decision to hold product manufacturers strictly liable in tort,[162] the parameters of the doctrine remain in flux. Federal legislation threatens to restrict the doctrine to harm from nongeneric risks.[163] Conflicts and uncertainties in the common law of product liability as it has evolved in the states have been cited as a major justification for federal action.[164]

The case for salvaging some remnant of strict liability within the area of generic product risks is not an easy one. The use of a policy-based analysis, however, makes it possible to link the accepted view that the rule should apply to construction defects to the admittedly controversial proposition that harm from unknown or unknowable generic risks should be compensated in the same fashion. The advantage of this approach is that it provides a coherent, principled basis for excluding other kinds of generic product risks from a rule of strict tort liability. Both the satisfaction of justifiable expectations on the part of product victims and the achievement of modest advances in safety justify the application of strict liability to harm from unknowable generic hazards.

Neither section 402A and comment k, interpreted as denying strict liability for unknowable generic risks, nor *Beshada*, forthrightly permitting recovery in such cases, presents a satisfactory resolution to the problem. The proposed federal Product Liability Act uncritically accepts comment k,[165] while *Beshada* has provoked an outpouring of criticism.[166] The tide at the moment apparently is running against strict liability in generic-risk cases. But the last words have not yet been spoken.

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[159] For one example of how generic risks may endanger bystanders, see P. Brodeur, Asbestos and Enzymes 25 (1972) (report that wives of seven asbestos workers who had regularly brushed their husbands' work clothes died from mesothelioma, a cancer associated with exposure to asbestos dust).

[160] See text accompanying note 146 supra.

[161] This conclusion is based on the assumption that airplanes do not regularly fly over the house.

[162] Greenman v. Yuba Power Prods., Inc., 59 Cal. 2d 57, 377 P.2d 897, 27 Cal. Rptr. 697 (1962).

[163] See note 14 supra.

[164] See S. Rep. No. 670, 97th Cong., 2d Sess. 3-10 (1982).

[165] See S. 44, 98th Cong., 1st Sess. § 5(e), 129 Cong. Rec. S285 (daily ed. Jan. 26, 1983):

> A product is not unreasonably dangerous in design or formulation if the harm was caused by an unavoidably dangerous aspect of a product. As used in this paragraph, an "unavoidably dangerous aspect" means that aspect of a product which could not, in light of knowledge which was reasonably accepted in the scientific, technical, or medical community at the time of manufacture, have been eliminated without seriously impairing the effectiveness with which the product performs its intended function or the desirability, economic and otherwise, of the product to the person who uses or consumes it.

See also S. Rep. No. 670, 97th Cong., 2d Sess. 30 (1982) (accompanying S. 2631, 97th Cong., 2d Sess., 128 Cong. Rec. S6846 (daily ed. June 16, 1982), a bill with a section virtually identical to this section of S. 44).

[166] See Schwartz, supra note 111, at 824-25; Schwartz, The Post-Sale Duty to Warn: Two Unfortunate Forks in the Road to a Reasonable Doctrine, 58 N.Y.U. L. Rev. 892, 901-05 (1983); Wade, supra note 99, at 738-39, 744; Comment, Requiring Omniscience: The Duty to Warn of Scientifically Undiscoverable Product Defects, 71 Geo. L.J. 1635 (1983); Birnbaum & Wrubel, N.J. High Court Blazes New Path in Holding a Manufacturer Liable, Nat'l L.J., Jan. 24, 1983, at 24, col. 1; Platt & Platt, Moving from Strict to "Absolute" Liability, Nat'l L.J., Jan. 17, 1983, at 18, col. 3.

For a defense of *Beshada* by the attorneys for the plaintiffs in the case, see Placitella & Darnell, *Beshada v. Johns-Manville Products Corp.*: Evolution or Revolution in Strict Products Liability?, 51 Fordham L. Rev. 801 (1983).

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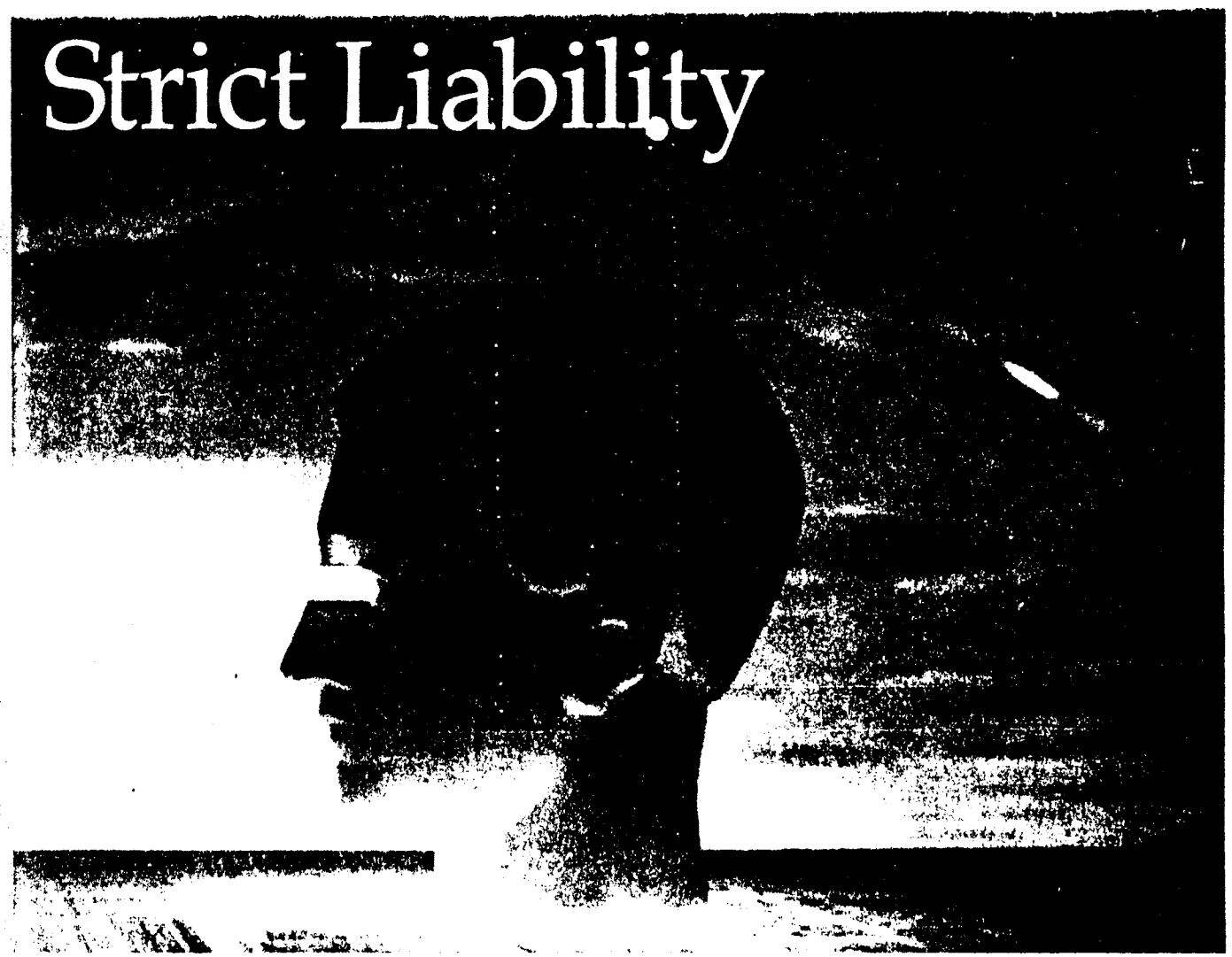
Strict Liability



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by Bill Wagner

Strict Liability Isn't a Problem—It's a Solution

Nobody likes to be sued. It's one of life's few absolute truths. For a manufacturer, litigation can be an expensive diversion of time and energy, and insuring against liability represents a significant cost of doing business. Another absolute truth, however, is that defective products injure and kill people. Product liability lawsuits have become a primary means by which injured victims seek redress from those who make and market defective products. It is fair to ask whether this system of dealing with defective products has helped or hurt society as a whole.

A recent report issued by the Conference Board asserts that strict liability has inhibited the development of new products, imposed heavy costs on corporate manufacturers and executives, and placed obstacles in the path to competitiveness.[1] The most interesting aspect of this report is its ancestry. In 1987, the board issued *Product Liability: The Corporate Response*.[2] That report, based on responses by the risk managers of major U.S. corporations, concluded that product liability had had "relatively little impact" on product prices, but has motivated improvements in product quality and safety. Understandably, lobbyists for tort reform were highly critical of the report. In response to their political concerns, the Conference Board undertook a new survey, this time of chief executive officers.[3] The result, predictably, hews much closer to the tort reformers' party line.

Not surprisingly, most of the CEOs polled would like to eliminate strict liability. An objective look at this doctrine, however, reveals that strict liability has served the American people well. Moreover, it is a doctrine that operates within the free enterprise system by providing economic incentives for safety, rather than by imposing massive governmental regulation or subsidized compensation programs.

The fact is that manufacturers, like many businesses, government entities and health care providers, are not victims of the tort system. They are experiencing serious problems because they have been mistreated by their own liability insurers. Through mismanagement and, perhaps, deliberate misconduct, the insurance industry has created a crisis in the cost and availa-

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Most CEOs would like to eliminate strict liability

bility of insurance. Changing the civil justice system will deprive injured victims of their rights, and it will reduce the incentive for safety that benefits us all. But it will not make liability insurance more affordable or available.

As a legal doctrine, strict liability does not represent a problem for American society; it is a solution.

What Strict Liability Is and Isn't

The starting point for any discussion of the merits of strict liability must be a clear understanding of what the doctrine means. Indeed, much of the hostility to the doctrine stems from confusing strict liability with absolute liability. Consider the following definition of strict liability in the Conference Board's CEO report:

> Strict Liability: A broad principle of product liability law which holds that a manufacturer is responsible for the torts (wrongful acts for which suits may be brought) that its product produces, regardless of whether the product was made properly when entered into the stream of commerce. In other words, this principle establishes liability without the showing of fault.

That sounds as if strict liability demands that a manufacturer pay for any harm caused by his or her product. Small wonder that the heads of 500 manufacturing firms strongly condemned such a doctrine. The problem is that the above statement is not the law in any American jurisdiction.

The most authoritative statement of the doctrine of strict liability is set forth in *Restatement (Second) of Torts* Section 402A, promulgated by the American Law Institute in 1965. Thirty-seven states have expressly adopted 402A; most of the remaining states apply rules that are substantially similar to it. The exact text of section 402A is worth examining:

> (1) One who sells any product in a defective condition unreasonably dangerous to the user or consumer or to his property is subject to liability for physical harm thereby caused to the ultimate user or consumer, or to his property, if
>
> (a) the seller is engaged in the business of selling such a product, and
>
> (b) it is expected to and does reach the user or consumer without substantial change in the condition in which it is sold.
>
> (2) The rule stated in Subsection (1) applies although (a) the seller has exercised all possible care in the preparation and sale of his product, and (b) the user or consumer has not bought the product from or entered into any contractual relation with the seller.

The comments issued by the institute are generally deemed authoritative in defining the scope of the rule. They make it clear that strict liability does *not* make manufacturers absolutely liable for any harm their products might cause. Only *defective* products result in liability:

> The rule stated in this Section applies only where the product is, at the time it leaves the seller's hands, in a condition not contemplated by the ultimate consumer, which will be unreasonably dangerous to him. The seller is not liable when he delivers the product in a safe condition, and subsequent mishandling or other causes make it harmful by the time it is consumed. The burden of proof that the product was in a defective condition at the time it left the hands of the particular seller is upon the injured plaintiff. ... (comment g).
>
> A product is not in a defective condition when it is safe for normal handling and consumption. If the injury results from abnormal handling ... the seller is not liable. (comment h).
>
> The rule stated in this Section applies only where the defective condition of the product makes it unreasonably dangerous to the user or consumer. ... The article sold must be dangerous to an extent beyond that which would be contemplated by the ordinary consumer who purchases it, with the ordinary knowledge common to the community as to its characteristics." (comment i).
>
> There are some products which, in the present state of human knowledge, are quite incapable of being made safe for their intended and ordinary use. [For example, many drugs and vaccines] ... The seller of such products, again with the qualification that they are properly prepared and marketed, and proper warning is given, where the situation calls for it, is not to be held to strict liability for unfortunate consequences attending their use, merely because he has undertaken to supply the public with an apparently useful and desirable product, attended with a known but apparently reasonable risk. (comment k)

Clearly, it is only the manufacturer of a *defective* product who will be strictly liable for the harm caused. In the controversial area of design defects, juries may impose liability only where the danger is unreasonable, either because it exceeds consumer expectation under comment i, or where the likelihood of serious harm out-

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weighs the usefulness of the particular design.[4] Though the precise definition of product defect has been the subject of a great deal of scholarly debate over the years, no American court has held a manufacturer liable for a non-defective product merely because it has caused injury.

Those who advocate replacing strict liability with a fault-based system simply misconceive the nature of strict liability as a legal doctrine.[5] Strict liability *is* based on fault.[6] Under negligence principles, the injured plaintiff bears the very difficult burden of proving that the actions of the manufacturer fell below the relevant standard of care.[7] Strict liability merely shifts the focus from the unreasonable conduct of the manufacturer to the unreasonable condition of the product.[8] It is the marketing of an unreasonably dangerous product which constitutes fault under strict liability. As a practical matter, it is difficult to conceive of an unreasonably dangerous product that could not also be linked to lack of due care, provided that the manufacturer recorded the process and the plaintiff had full access to the company's information.[9]

Another fact that should not be overlooked is that strict liability was not invented with the promulgation of the *Restatement* in 1965. Under the common law of sales, and then under the Uniform Commercial Code, sellers have historically been held strictly liable for breach of warranty. Injured purchasers have always been entitled to sue the seller of a product that was not reasonably safe. The difficulty was that contract law required privity between the plaintiff and the defendant.[10] One who was injured by a defective automobile could bring an action against the dealer, but not the manufacturer of the car. Food and drug products were generally exempt from the privity rule.[11] It is worth remembering that, prior to strict tort liability, the makers of vaccines were held strictly liable for breach of warranty without privity.[12]

Generally speaking, the adoption of strict liability in tort did not impose higher standards on U.S. manufacturers than existed in theory, at least, under negligence or warranty.[13] Strict liability simply removed the artificial barriers that allowed manufacturers to evade liability for unsafe products.

Toward a Safer Society

The purposes of strict liability, which it shares with tort law in general, are to deter the marketing of unsafe products and to compensate victims who are injured by unsafe products.[14] It accomplishes these goals by imposing on those who have greatest control over the safety of products, and who reap the profits from their sale, the cost of injuries caused by defective products.[15] This system of introducing safety incentives into the marketplace not only benefits the injured plaintiff, but fosters a safer society for all consumers through the mechanism of the marketplace itself.

The fundamental genius of tort law is that it uses the natural economic forces of the free market system to further the goals of safety. Suppose, for example, that Company *A* equips its industrial machine with an interlock device to prevent injury to operators of the machine, at an added cost of $50 per unit. Rival Company *B* sells a similar machine without such protection. In the absence of tort liability, *B* enjoys an unfair competitive advantage due to its lack of investment in safety. By forcing *B* to compensate workers who are injured due to the

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It's a Solution

(continued from page 15)

lack of, for example, a guard, strict liability adds to the cost of *B*'s machine. The greater the hazard, the greater the reward for the safety conscious manufacturer. Products liability does not force any manufacturer to take its product off the market; it demands only that the product pay for the harm its defects cause. In a competitive market, strict liability enables the safest products to drive out the most dangerous.[16]

It should be recognized that "private" safety enforcement through tort actions is a conservative means for dealing with product injuries. The alternative to liability is not necessarily less restriction. Accountability of some kind is the rule in our society; immunity the rare exception. If this private remedy were withdrawn, there would undoubtedly be great public pressure for massive governmental regulation and civil and criminal penalties against the makers of unsafe products.

Secondly, immunity from tort liability would not "save" the money that would otherwise go to plaintiffs. It would simply shift the costs of injury to other compensation mechanisms which do not provide the same incentive for safety. Consider, for example, the fact that more than half of product liability claimants are workers injured on the job. What is often overlooked is that manufacturers are also employers and consumers of the products of many other companies, from manufacturing machines to office equipment to delivery trucks. Any reduction in product liability insurance premiums would be offset by immediate increases in costs for workers compensation and other insurance benefits as the right of subrogation disappeared. If such benefits were to become the sole source of compensation for injured workers and their families, there would inevitably be enormous, maybe irresistible political pressure to dramatically increase the benefits and coverage of these programs.[17]

For manufacturers, elimination of the tort remedy would result in shifting money from one expense (e.g., liability insurance premiums) to another expense (workers compensation, medical insurance, disability and other insurance premiums). For society as a whole, the consequences are more disturbing because it shifts the burden of paying for the harm caused by defective products away from the entity which is most able to eliminate the danger in the first place.

Manufacturers may rail against the imposition of strict liability in tort, but few would favor the most likely alternative to the tort system: deterrence through government regulation, and compensation through a genuinely no-fault insurance scheme. Moreover, society as a whole would lose a doctrine that has advanced safety.

Is America a safer place than it would have been without strict liability? There can be no doubt of it.

There are many examples of dangerous products that were only made safer after the manufacturer was held liable to a victim injured by the product. A classic example, among literally hundreds, is the hot water vaporizer that tended to tip over, pouring scalding water near sleeping children. Only after being held liable did the maker install the simple device of a secure lid.[18] Similarly, it was liability that motivated the maker of drain cleaner to use a safe container.[19] Professor Tom Lambert has collected many other instances of product liability resulting in product safety.[20]

But by far the greatest progress toward a safe society is due to the *preventive* impact of products liability. Manufacturers have learned that it is better to build a fence at the top of the cliff than provide an ambulance below. The Conference Board survey of risk managers indicates a dramatic increase in the number of companies that have instituted product safety programs.[21] Even the survey of CEOs reveals that more than half the companies have improved the safety of their products due to the pressure of potential liability.[22] The Consumer Federation of America has concluded that improved product safety has saved billions by preventing injury and death.[23] It is no exaggeration to state that strict liability lawsuits are primarily responsible for that progress.

Chilling Development?

In the debate over whether strict liability has been good for America, the question of whether it "chills technological innovation" is not particularly helpful. First, the question assumes that every decision not to develop or produce a product is a loss to society. Surely the decision not to produce a toy that fires sharp projectiles or a mascara that can cause blindness is not to be regretted. The very purpose of strict liability is to deter the marketing of unsafe products. One might as well ask whether laws against negligent operation of automobiles have a chilling effect on driving. Second, the question overlooks the fact that improvements in product safety are themselves technological innovations. It is the liability incentive that leads companies to apply technology to safety.

As noted above, strict liability does not demand that manufacturers produce absolutely injury-proof products. It only asks that, while the company is spending considerable sums to determine whether its product will sell, it also investigate whether the product could kill; that in designing a product that does its job well, engineers also focus their expertise on whether the product does its job safely; that a corporation investing in advertising to persuade consumers to buy their product also invest a small amount in warning them of the dangers associated with it. Is that too much for the law to ask? There is absolutely no indication that manufacturers are unable to make reasonably safe products. Instead, the primary complaint made

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by the CEOs polled by the Conference Board is that product liability insurance, even for companies with few claims against them, is often too expensive or not available at all. In other words, it is not product reliability but insurance reliability that is hindering progress.

"Competitiveness" has become a buzzword in these days of high trade deficits. So it is not surprising to find that term creeping into the rhetoric of the tort reformers. But the charge that strict liability hampers competitiveness has no basis in fact or reason.

Trade is, of course, a two-way street. Half of the equation concerns imports. American auto makers, for example, have lost a considerable share of the domestic market. But any loss in competitiveness is not due to strict liability. Japanese, German and other foreign car makers are subject to the same strict liability rules as the American Big Three. The courtroom is a level playing field.

On the other side of the equation, the reasons why American manufacturers find it difficult to export more goods are varied and complex. The notion that American products are too safe to be competitive borders on nonsense. It is true that the steps manufacturers have taken to improve product safety as a result of strict liability do add to the cost of products. However, quality and safety, like price, are competitive factors. It is worth noting that many of the auto imports sold in the United States are more expensive than American models. In addition, other countries, particularly the developed countries where most American manufactured goods are exported, also impose safety standards. Finally, it should be recognized that the types of products in which American manufacturers have become less competitive, such as electronics, clothing and textiles, are those which have fairly low product liability exposure.

Again, the Conference Board's CEO survey reveals that the manufacturers' chief complaint is not that strict liability requires American goods to be excessively safe. It is that their liability insurance premiums are excessively high.

Amazingly, few manufacturers appear to question the justification for huge premium hikes or policy cancellations. They have adopted the mythology promoted by their insurers: that the tort system is running out of control, forcing insurers to charge higher premiums to cover their costs or cancel policies because the risks are unpredictable. In short, they have accepted as fact one of the most successfully promoted myths in public relations history: The Lawsuit Crisis.

The Lawsuit Crisis Myth

There is little doubt that product manufacturers have been suffering through an insurance crisis. Particularly in the mid-1980s, premiums increased several hundred percent. All too often, insurance was not available at any price, even for companies that experienced few claims. What was the true cause of this crisis?

The insurance industry has claimed that too many plaintiffs are suing for injuries, that runaway juries are awarding inordinately high verdicts, and that insurers are simply passing along the high cost of the tort system. In other words, "Blame the victims, blame the juries, and most especially, blame the lawyers."

It is worth remembering that a similar crisis gripped the industry in the mid-1970s. A presidential task force studied the facts and concluded that rate increases were far in excess of genuine liability. The legal study commissioned by the task force determined that "the volume and size of damage awards in all probability cannot be considered the direct cause of the alleged insurance problems."[24] Moreover, "no inequitable doctrine or group of doctrines could produce a greater availability of or a lower cost of insurance."[25] The facts demonstrate that the latest crisis is also not due to the tort system.

The insurance industry has claimed so often and so loudly that Americans are becoming litigation-happy and that juries give away huge sums to any claimant, that there is a danger that the "litigation explosion" may have achieved the status of conventional wisdom by sheer repetition. Industry spokesmen have reinforced this perception to the media by distorting the facts of a few unusually large verdicts. The Reagan administration added a measure of false credibility to the myth by adopting it unquestioningly in a report prepared under the direction of then Attorney General Edwin Meese.[26] The Working Group made no independent investigation of the facts. Its conclusion that the number of suits is growing was based entirely on the increase in the federal court caseload. The conclusion that verdicts are skyrocketing was based on statistics concerning "average" verdicts published by Jury Verdict Research.

The fact is that the number of lawsuits has not been increasing much faster than population growth. A report by the General Accounting Office concluded that the statistics relied upon by the Working Group revealed that most of the growth in the caseload was attributable to the atypical surge of asbestos, bendectin and Dalkon Shield cases, situations in which many years of exposure and injury have resulted in a sudden wave of cases. Apart from those unusual cases, the products liability caseload has been increasing at about 4 percent annually since 1981, about the same rate of increase as the gross national product and slightly above the rate of population increase. The GAO concluded that the growth in products liability suits in general "appears to be neither accelerating nor explosive."[27] More important, approximately 95 percent of products liability actions are in state court where the National Center for State Courts has found that "careful examination of current trial data ... provides no evidence to support the existence of a national 'litigation explosion' in the

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state trial courts."[28] There is simply no reliable evidence that products liablity lawsuits are increasing to an extent that would justify increases of several hundred percent in liability premiums.

The myth of runaway jury verdicts is equally false. The Working Group relied on the average verdict in a relatively small number of newsmaking cases. In testimony before Congress, the chairman of Jury Verdict Research himself repudiated the abuse of these statistics. "JVR has neither asserted nor published any conclusions that the average size of jury verdicts has recently skyrocketed," he testified. "Although verdicts, as well as many other items, have increased substantially over the years, our studies do not support any claim of recently escalating jury awards."[29]

Equally significant is a closed-claim study by the insurance industry that refutes the unsupported claim that the largest awards are increasing the fastest. In a study of claims over $100,000 (about 1 percent to 2 percent of total claims) including verdicts and settlements, payments for bodily injury increased about 15 percent per year, compared to the average cost of living increase of 10 percent.[30] What is crucial to keep in mind is that bodily injury payments are primarily influenced by the cost of medical care, which has increased faster than inflation. During the same period, hospital costs rose an average of 18 percent annually, and general medical costs rose 12.5 percent per year. Again, these increases cannot justify the huge hikes in premiums. Nor could they explain the sudden unavailability of insurance for many customers. The real cause of the insurance crisis lies with the insurance industry itself.

Cash-Flow Underwriting

The notion that large premium increases necessarily reflect large increases in payments to plaintiffs has a superficial appeal to those who are accustomed to thinking of insurance as essentially an underwriting operation, estimating risk and collecting enough in premiums to cover payouts plus overhead and reasonable profits.

In reality, insurers receive a substantial amount of income by investing premium dollars. This is especially true in products liability, where claims may not be paid until many years after the premium has been collected. Since the actual demand for this type of insurance is relatively static, it is often the investment side which drives the industry. As a result, liability insurers experience business cycles which reflect the investment environment in the economy.

Insurers tend to magnify the effect of investment cycles by letting short-term investment opportunity, rather than risk assessment, set premium rates. In the early 1980s, for example, with the prime rate exceeding 20 percent, insurers engaged in a price war, slashing premium rates in an effort to attract more premium dollars to invest. Companies expected investment income to offset the fact that the premiums were potentially insufficient to cover anticipated liability. This so-called "cash flow underwriting" reached absurd dimensions with the advent of retroactive insurance. For example, a group of insurers wrote liability coverage for the fire at the MGM Grand Hotel in Las Vegas, *after* the hotel had burned down.[31] As the Insurance Services Office reported:

> For the better part of seven years, the insurance industry has been engaged in a brutal price war. During the early 1980s the price for commercial insurance was decreasing, sometimes sharply, as insurers vied for premium dollars to invest at the high interest rates then in effect. At the time, commercial customers did not complain. Indeed many realized that commercial insurance in the United States was being sold at below cost, even when investment income was considered.[32]

In 1984, interest rates plunged to around 9 percent. Insurers suddenly believed that their reserves were inadequate to meet anticipated liabilities and that investment income would no longer bridge the gap. What followed was a panic of cancellations and price hikes in an effort to balance the books. This latest cycle was made particularly severe by reinsurers.

In the 1980s, an American insurer might sell products liability coverage of up to $50 million, but pay a reinsurer to assume the liability above $10 million. In this way, the primary insurer could write a greater volume of primary insurance and still remain within the 3-to-1 premium to surplus ratio imposed by statute or sound accounting practice. These reinsurers were primarily foreign entities wholly outside the regulatory powers of the states. At one point Lloyds of London was writing 25 percent of the American reinsurance market.

When interest rates plunged, it was the reinsurers, with their long-tail coverage, who were affected first and hardest. Many defaulted on their obligations. Lloyds substantially pulled out of the American market. The effect was to dramatically strain the capacity of the American companies, who were already beginning to feel the effects of investment shortfalls. Again, the companies resorted to cancelling or reducing coverage and jacking up premiums to bring capacity into line with the 3-to-1 ratio.[33]

It is clear that abusive cash flow underwriting, especially when combined with dependence on foreign reinsurers, turned a cyclical downturn into a crisis.

There are two lessons to be learned from this experience. The first is that premium increases are strongly influenced by investment returns, or, more precisely, anticipated return on investment of premiums. The operation of the tort system has had relatively little impact.

The second lesson is that the industry's response to the market downturn

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was to protect its profits, not its policy holders. Businesses were hit with huge premium increases, reduced coverage, and even cancellation, so that the industry would not fail to increase profits for even a single year. In 1985, the property casualty industry took in $2.1 billion in net profits; in 1986, it earned $13.1 billion.[34] As the General Accounting Office reported to Congress, the industry managed to earn almost $75 billion between 1976 and 1985, on which it paid virtually no income tax, and expected to gain $90 billion between 1989 and 1990.[35] In effect, the policyholders have been insuring the profits of the insurance industry.

Not only did the property-casualty insurance industry manage to turn a crunch into a crisis with its abusive practices, the industry may have been guilty of deliberately fomenting the crisis from the start.

The Insurance Information Institute embarked on a $6.5 million media campaign to sell to the public the idea that the insurance crisis was really a lawsuit crisis.[36] In this fashion, the industry not only deflected criticism of its own role in the crisis, but also created a panic atmosphere in the state legislatures. Under the guise of "tort reform," legislatures were enticed into showering special benefits on the healthy insurance industry that far surpass any bailout given to failing companies.

Soon after the insurance crisis became part of the national consciousness, there were indications that elements in the insurance industry were deliberately worsening the crisis in order to panic legislatures into adopting tort reform statutes. In June 1985, John J. Byrne, now Chief Executive Officer of Fireman's Fund, told a meeting of the Casualty Actuaries of New York, "It is right for the industry to withdraw and let the pressures for reform build in the courts and in the legislatures."[37] He also noted that "withdrawing from certain lines such as product liability ... will eventually bring home the message to state and federal lawmakers."[38]

Tort Reform Won't Work

A set of proposals has been pressed upon the legislatures and the public under the guise of "reforming" the tort system. The proposals favored by the CEOs in the Conference Board poll closely match the most commonly urged measures outlined in the Working Group Report. Limit non-economic and punitive damages, abolish joint and several liability, abolish the collateral source rule, mandate periodic payment of future damages, and limit attorney's fees.

The most objectionable characteristic of these proposals is that they limit the rights of victims to obtain compensation for their injuries. Even if these provisions would alleviate the high cost of liability insurance, it is unconscionable to require the most severely injured persons to subsidize a benefit for American business.

The fact is, however, that none of these proposals has any chance of relieving manufacturers of the burden of the insurance crisis. The underlying premise of the various proposals is that, by reducing the amounts that liability insurers must pay to injured victims, the insurers will save substantial sums that they will pass along to policyholders in the form of lower premiums.

Manufacturers should ask themselves whether the insurance industry, which milked huge profits from policyholders during the crisis, would be likely to pass along any savings achieved through tort reform. If past performance teaches anything, it is that this money will go directly to the insurance companys' coffers and stay there.

Moreover, most of the proposals, while devastating to some injured victims, will not result in a substantial savings to insurers. The industry itself has admitted that this package of reforms will have little or no impact on claims payments.

More fundamentally, as demonstrated above, there is no relation between the civil justice system and the unavailability and unaffordability crisis in insurance. Premiums rose in the mid-1970s, fell in the early 1980s, and rose again in the mid-1980s, a mirror image of the investment market. The tort system did not cause these cycles, and changing the rules of tort liability will not stop them.

Time and again, in state after state where tort reform was considered by the legislature, insurers were unwilling to couple their support for restrictive legislation with a promise to reduce premiums if the measures were enacted. In testimony before Congress, insurers have stated that enactment of restrictive tort bills will not result in lower rates or a greater availability of coverage. On this matter, at least, manufacturers should take their insurers at their word.

Conclusion

Strict liability for unreasonably dangerous defective products has given us a safer society. It has done so by providing market incentives for safety, free from the heavy hand of government regulation and massive compensation programs. Some manufacturers are facing problems in developing new products or competing in world markets, not because the law requires American products to be reasonably safe, but because liability insurance is costly or unavailable.

There is an anecdote about a drunk who one night dropped his keys in his dark doorway, but went looking for them under the street lamp, "because the light's better out here." The tort system may be an easy target, but it is the wrong target. What we need to solve the liability insurance crisis is more light on the insurance industry and a willingness to hold that immensely important industry accountable for its conduct.

Footnotes

1. CONFERENCE BD., THE IMPACT OF PRODUCT LIABILITY (1988).

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2. CONFERENCE BD., PRODUCT LIABILITY: THE CORPORATE RESPONSE (1987).

3. CONFERENCE BD., *supra* note 1

4. This risk-utility analysis was widely adopted from Wade, *On the Nature of Strict Tort Liability for Products*, 44 MISS. L.J. 825 (1973). Even the few courts that have eliminated the term "unreasonably dangerous" from jury instructions still apply a balancing test to distinguish unacceptably dangerous products from those that are merely dangerous. *See* Barker v. Lull Eng'g Co., 573 P.2d 443 (Cal. 1978).

5. "Replacement of strict liability with a fault-based system" was at the top of the CEOs' list of desired tort reforms. CONFERENCE BD., *supra* note 1, at 27.

6. The current reporter for the Restatement, who was active in the adoption of 402A, has stated: "I am convinced that even if no mention had ever been made of the concept of strict liability, the present state of the law as based on negligence would be very close to what it is today." Wade, *An Evaluation of the "Insurance Crisis" and Existing Tort Law System*, 24 HOUS. L. REV. 81 (1987).

7. Even before the advent of strict liability, courts were working to resolve the injustice of requiring the injured plaintiff to prove facts wholly within the control of the defendant. Indeed, it was a case applying the doctrine of *res ipsa loquitur* to relieve the victim of an exploding bottle of the burden of proving the bottler's specific negligent conduct that occasioned Judge Traynor's initial call for strict tort liability in Escola v. Coca-Cola Bottling Co., 150 P.2d 436 (Cal. 1944)(concurring).

8. *See, e.g.*, Suter v. San Angelo Mach. Co., 406 A.2d 140 (N.J. 1979).

9. Wade, *Evaluation*, *supra* note 9 (current law concerning both design defect and inadequate warnings are "very similar to negligence").

10. *See* Prosser, *Assault Upon the Citadel*, 90 YALE L.J. 1099 (1960); Prosser, *Fall of the Citadel*, 50 MINN. L. REV. 791 (1966).

11. *See* Prosser, *supra*; and James, *Products Liability*, 34 TEX. L. REV. 43 (1955).

12. Gottsdanker v. Cutter Laboratories, 6 Cal. Rptr. 320 (1960)(polio vaccine).

13. *See, e.g.*, Rheingold, *Expanding Liability of Product Suppliers*, 2 HOFSTRA L. REV. 521 (1974)(adoption of strict liability had no appreciable effect on consumers or plaintiff's lawyers); BEASLEY, PRODUCT LIABILITY AND THE UNREASONABLY DANGEROUS REQUIREMENT 303-39 (1981) (survey of jurisdictions which had not adopted strict liability, concluding that nearly all imposed the same duty on manufacturers under warranty without privity). William Prosser, the chief architect of *Restatement* Section 402A, readily acknowledged that the shift from warranty to strict liability made little change in what was required of sellers. Prosser, *Fall*, *supra* note 10.

14. *See* A.B.A. Special Committee on the Tort Liability System, Toward a Jurisprudence of Injury: The Continuing Creation of a System of Substantive Justice in American Tort Law ch. 4 (1984).

15. *See* Greenman v. Yuba Power Prods., 377 P.2d 897 (Cal. 1963). In macroeconomic terms, the manufacturers of products are generally the "cheapest cost avoider" in terms of accident prevention. *See* G. CALIBRESI, THE COSTS OF ACCIDENTS 135 (1970).

16. A recent economic analysis of tort law confirms the view that tort liability generally provides the incentives for the most efficient and cost-effective allocation of the costs of accident. W. LANDES & R. POSNER, THE ECONOMIC STRUCTURE OF TORT LAW (1978).

17. For a proposal to rely heavily on first-party compensation schemes, see Priest, *The Current Insurance Crisis and Modern Tort Law*, 96 YALE L.J. 1521 (1987). Interestingly, even this critic of the tort system rejects the assertion that the crisis in cost and availability is due to an increase in the number and size of awards.

18. McCormick v. Hankscraft Co., 278 Minn. 322, 154 N.W.2d 488 (1967).

19. Moore v. Jewell Tea Co.,253 N.E.2d 636 (Ill. App. 1969), *aff'd*, 263 N.E.2d 103 (Ill. 1970).

20. Lambert, *Suing for Safety*, TRIAL, Nov. 1983, at 48.

21. Risk managers reported that improved warnings and product safety were two of the most common responses to the threat of liability. CONFERENCE BD., *supra* note 2, at 14.

22. The CEOs responding indicated that nearly half the companies with products liability experience had improved warnings and a third improved the design of the product to make it safer. CONFERENCE BD., *supra* note 1, at 18.

23. COOPER, THE BENEFITS OF THE MODERNIZATION OF THE TORT LAW IN THE CONTEXT OF THE SOCIAL MOVEMENT FOR IMPROVED SAFETY AND QUALITY IN THE NATIONAL ECONOMY (1987).

24. U.S. DEPARTMENT OF COMMERCE INTERAGENCY TASK FORCE ON PRODUCT LIABILITY, LEGAL STUDY, at III-131-32.

25. *Id.*, at III-118. For a retrospective analysis on the product liability "crisis" of the 1970s, see Page and Stephens, *The Product Liability Insurance "Crisis": Causes, Nostrums and Cures* 113 CAP. U.L. REV. 387 (1983).

26. U.S. DEP'T OF JUSTICE, REPORT OF THE TORT POLICY WORKING GROUP ON THE CAUSES, EXTENT AND POLICY IMPLICATIONS OF THE CURRENT CRISIS IN INSURANCE AVAILABILITY AND AFFORDABILITY (1986).

27. U.S. GEN. ACCOUNTING OFFICE, PRODUCT LIABILITY: EXTENT OF "LITIGATION EXPLOSION" IN FEDERAL COURTS QUESTIONED (Jan. 1988).

28. NAT'L CENTER FOR STATE COURTS, 1986 ANNUAL REPORT 173 (JULY 1986). In 1987, the RAND Corp. Institute for Civil Justice issued a special report that correlates information from both the NCSC study and its own data. Its conclusion: "Whatever the slight differences among estimates, it is clear that the amount of tort litigation nationwide is growing relatively slowly." RAND CORP. INSTITUTE FOR CIVIL JUSTICE, TRENDS IN TORT LITIGATION: THE STORY BEHIND THE STATISTICS 6 (1987).

29. *Hearing Before the Subcomm. on Economic Stabilization of the House Committee on Banking, Finance and Urban Affairs*, 99th Cong., 2d Sess. 25 (Aug. 6, 1986)(statement of Philip J. Hermann, Chairman of the Board, Jury Verdict Research, Inc.).

30. ALLIANCE OF AMERICAN INSURERS, AMERICAN INSURANCE ASSOCIATION, A STUDY OF LARGE PRODUCT LIABILITY CLAIMS CLOSED IN 1985 (1986). The RAND Corp. Institute for Civil Justice has estimated that the average claim paid by general liability insurers, which includes product liability claims, increased 18 percent annually from 1979 to 1984. RAND CORP. INSTITUTE FOR CIVIL JUSTICE, COSTS AND COMPENSATION PAID IN TORT LITIGATION 144 (1986).

31. *See* BUS. INS., Jan. 10, 1983, at 9.

32. INS. SERVICES OFFICE, FINANCIAL CONDITION OF THE INDUSTRY—AN UPDATE (1985).

33. *See* NATIONAL INSURANCE CONSUMERS ORGANIZATION, FACTS ON REINSURANCE (1986).

34. INSURANCE INFORMATION INSTITUTE, INSURANCE FACTS: PROPERTY CASUALTY FACT BOOK (1986-87, 1987-88 eds.).

35. *Hearing Before the Subcomm. on Oversight of the House Committee on Ways and*

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Means, 99th Cong., 2d Sess. 4-71 Apr. 28, 1986)(statement of Johnny C. Finch, Senior Associate Director, General Accounting Office).

36. The Insurance Information Institute, the public relations arm of the industry, announced a massive "effort to market the idea that there is something wrong with the civil justice system in the United States." NAT'L UNDERWRITER, Dec. 21, 1984, at 1, 2, 46. That effort included a $6.5 million national advertising campaign that Institute claimed would "change the widely held perception of an insurance crisis to a perception of a lawsuit crisis." J. COM., Mar. 19, 1986, at 1, 20. This deliberate effort to sell the public and legislatures on the notion of a lawsuit crisis is well documented in NAT'L INS. CONSUMER ORG., AND NOW THE REAL FACTS: A RESPONSE TO THE INSURANCE SERVICES OFFICE'S 'INSURER PROFITABILITY—THE FACTS' (1986) and *The Manufactured Crisis: Liability Insurance Companies Have Created a Crisis and Dumped It on You*, CONSUMER REP., Aug. 1986, at 544.

37. J. COM., June 18, 1985.

38. BEST'S INS. MGMT REP., June 24, 1985.

39. In nearly all types of claims tested, "the impact of the changes generally ranged from marginal to imperceptible." INS. SERV. OFFICE, CLAIMS EVALUATION IMPACT, NATIONAL OVERVIEW (1987).

Strict Liability

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case was *Thomas v. Winchester*,[10] in which a druggist mislabeled a bottle of extract of belladonna (a deadly poison used in quite small quantities for heart trouble) as extract of dandelion, a harmless medicine that could be used in larger quantities. The plaintiff took a large dose and became quite ill. The court allowed recovery on the ground that the poison was imminently dangerous, so that the druggist owed a duty to the public in general and not just to a person in privity with him. This case produced other breakaway decisions,[11] based on differing rationales, which were collected, analyzed and organized by Judge Walter H. Sanborn in *Huset v. J.I. Case Threshing Machine Co.*[12] into a set of three exceptions to the privity requirement:

> [(1) an] act of negligence which is imminently dangerous to the life or health of mankind and which is committed in the preparation or sale of an article intended to preserve, destroy or affect human life, . . . [2] an obvious act of negligence which causes injury to one who is invited by him to use his defective appliance upon the owner's premises, and . . . [3] an act of selling an article which he knows to be imminently dangerous to life or limb to another without notice of its qualities.

Huset became a new point of departure and many later decisions were based on the exact language of Judge Sanborn.

In 1916, there came the famous case of *MacPherson v. Buick Motor Co.*[13] The facts were similar to *Winterbottom* in that a defective wheel of the vehicle (a Buick Model 10 Runabout) collapsed, injuring the driver. Declaring that "[p]recedents drawn from the days of travel by stage coach do not fit the conditions of travel today," Judge Benjamin N. Cardozo analyzed the earlier negligence cases, particularly those from New York,[14] and concluded that the many exceptions to the privity rule had eroded it to the point that the exceptions had become the general rule. *MacPherson* is the classic illustration of the method by which the law evolves gradually until a perceptive judge or commentator is able to demonstrate conclusively that the change has taken place and the exceptions are reversed.

Those of us who first read the opinion many years ago remember it as the beginning of the modern negligence law of products liability. In this we are correct, but we have been inclined to forget how cautious Cardozo was and how carefully he limited the extent of the change. Let me quote a few sentences from his decision:

> If the nature of a thing is such that it is *reasonably certain to place life and limb in peril when negligently made*, it is then a thing of danger. . . . If to the element of danger there is added knowledge that the thing will be used by persons other than the purchaser, and used without new tests, then irrespective of contract, the manufacturer of the thing of danger is under a duty to make it carefully. . . . There must be knowledge of danger, not merely possible, but probable. . . . There must also be knowledge that in the usual course of events the danger will be shared by others than the buyer. (italics added)

Most of the potential limitations suggested by Cardozo's cautious language have now been sloughed off. Thus, the requirement that "life and limb" be put in peril was soon regarded as being met by danger of any bodily injury, and eventually of any physical injury, even to property. The requirement that it be "reasonably certain" that the injured party's personal safety be put in peril came to be satisfied by a showing that the defendant had created an unreasonable risk. The requirement that the defendant have "knowledge that the thing will be used by persons other than the purchaser" came to be met by a finding of mere foreseeability that others might use the product. The requirement of "knowledge of danger not merely possible but probable" came to be met by simple foreseeability of the risk of harm. In other words, the potential limitations of *MacPherson* were rejected in favor of the general principles of negligence, with their customary attributes. Henceforth, in a negligence action for physical injury, lack of privity of contract, either vertical or horizontal, was no barrier to recovery.

The general principles of negligence law were soon expanded to new situations. The maker of a component part of a finished product was held to the same duty of care as the assembler of

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