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# Strict Liability in the Manufacture of Pharmaceuticals: The Halcion Homicide

*Martin J. MacNeill\**

## I. INTRODUCTION

In one of the first cases of its type, a woman from southern Utah and her dead mother's estate brought suit<sup>1</sup> for negligence and wrongful death against Upjohn, the maker of Halcion, the world's most prescribed sleeping pill.<sup>2</sup> The litigation is unique in that a user of Halcion, who admitted to killing her mother, sued the drug company for civil damages over the death.

On June 19, 1988, the fifty-eight-year-old plaintiff, Ilo Grundberg, without apparent provocation, shot her eighty-two-year-old mother eight times in the head and neck.<sup>3</sup> Mrs. Grundberg was arrested and charged with one count of second-degree murder.<sup>4</sup> As her primary defense, Grundberg argued that she suffered from an acute addiction to prescribed medication and that, at the time of her mother's death, Grundberg was temporarily insane due to a severe case of "Halcion intoxication."<sup>5</sup> On February 8, 1989, after hearing initial testimony, Utah's Fifth District Court Judge J. Philip Eves dismissed all charges against Grundberg, ruling that the killing was a result of her addiction.<sup>6</sup>

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\* B.S. 1975, St. Martin's College; D.O. 1983, College of Osteopathic Medicine of the Pacific; J.D. 1990, Brigham Young University, J. Reuben Clark Law School. This paper was awarded first place in the American Bar Association Tort and Personal Injury 1990 Writing Competition.

1. Grundberg v. Upjohn Co., No. 89-C-274-W (D. Utah filed Mar. 24, 1989). The suit, however, has been settled. See *Upjohn Settles Product Liability Suit Alleging Drug Led Woman to Shoot Mother*, 6 Toxics L. Rep. (BNA) 333-34 (Aug. 14, 1991) (terms are confidential). Two Halcion class action suits are pending against Upjohn in the Southern District of Ohio: *Wilson v. Upjohn*, No. C-1-89-346 (S.D. Ohio filed May 8, 1989) and *Farris v. Upjohn Co.*, No. C-1-89-553 (S.D. Ohio filed Aug. 14, 1989).

2. NAT'L L.J., Oct. 17, 1989 (LEXIS, Nexis, Omni File) ("The drug is the most widely used sleep medicine and is currently sold in more than 75 countries.").

3. United Press Int'l, Feb. 7, 1989 (LEXIS, Nexis, Omni file).

4. United Press Int'l, Mar. 25, 1989 (LEXIS, Nexis, Omni file).

5. *Drugmaker Sued in Shooting Death*, Chicago Tribune, March 26, 1989, at 14 (LEXIS, Nexis, Omni file).

6. Blum, NAT'L L.J., *Suit Blames Sleeping Pill For Murder*, Apr. 10, 1989, at 9 (LEXIS, Nexis, Omni file); United Press Int'l, *supra* note 3 ("involuntary intoxication is a viable defense

In filing the civil suit against Upjohn, Grundberg and her mother's estate argued that "the drug Halcion (triazolam) was unreasonably dangerous, unsafe for its intended use and defective because of its tendency to cause intoxication in the user, when used properly and according to the advice and directions supplied by the defendant [Upjohn]."<sup>7</sup> The plaintiffs further claimed that "[t]hese side effects, if not promptly discovered and treated, can lead to personal injury and death to the user and others in contact with the user."<sup>8</sup>

The lawsuit sought damages for Mrs. Grundberg's "personal injuries, physical and mental pain and suffering, emotional distress, false imprisonment, expenses and attorney's fees."<sup>9</sup> The decedent's estate also sought to recover compensatory and punitive damages for the wrongful death of Mrs. Grundberg's mother along with funeral and burial expenses.<sup>10</sup> Mrs. Grundberg and her dead mother's estate argued that Upjohn, as the manufacturer, knew or should have known of the drug's potential dangers.<sup>11</sup> Furthermore, the suit contended that Upjohn marketed Halcion at an excessive dosage.<sup>12</sup> This "excessive dose was consumed by plaintiff Ilo Marie Grundberg, proximately causing injury and damage to the plaintiff . . . as well as proximately causing the wrongful death of her mother . . ." <sup>13</sup> The suit claimed that Upjohn was strictly liable for the alleged product defect.<sup>14</sup>

The concept of strict liability eliminates the need to prove negligence for an injury caused by a defective product.<sup>15</sup> However, policy

[in the Grundberg case].")

7. Plaintiffs' Complaint at 5-6, *Grundberg v. Upjohn Co.*, No. 89-C-274-W (filed Mar. 24, 1989).

8. *Id.* at 6.

9. *Id.* at 15.

10. *Id.* at 18.

11. *Id.* at 6.

12. *Id.* at 7 (Upjohn "manufactured, distributed, and sold the drug Halcion . . . in a dangerous, excessive dose, far beyond any reasonable and responsible margin of safety . . .").

It is interesting to note that in October 1987, the Federal Drug Administration lowered the dosage recommended on the drug's label. Arieff, *Bizarre Side-Effects Trigger Review of Popular Sleeping Pill*, Reuter Libr. Rep., Sept. 19, 1989 (LEXIS, Nexis, Omni file). The Physician's Desk Reference of 1990 has also eliminated the 0.5mg dosing suggestions. Prior to 1989 the recommendation of the manufacturer was for 0.5mg per night. Compare PHYSICIAN'S DESK REFERENCE 2127-28 (42d ed. 1988) with PHYSICIAN'S DESK REFERENCE 2226-28 (44th ed. 1990). Unless otherwise noted, all references to the PDR will be to the 42nd edition of the Physician's Desk Reference published in 1988.

13. Plaintiffs' Complaint at 7.

14. *Id.* at 12 (Upjohn "was liable to the plaintiffs under strict liability for the injurious consequences to the [plaintiffs] proximately caused by the manufacture, sale and use of the product Halcion . . .").

15. *Greenman v. Yuba Power Prod.*, 59 Cal. 2d 57, 377 P.2d 897, 27 Cal. Rptr. 697 (1963) (Manufacturers should be strictly liable for products placed in the marketplace, knowing the product will not be further inspected, and possibly cause injury); Restatement (Second) of Torts §

interests have shaped the unique nature of pharmaceutical case law to provide multiple exceptions to the standard rules of strict liability. Some of the exceptions favor plaintiffs.<sup>16</sup> In such cases, manufacturer liability is easier to prove and is often decided with minimal evidence.<sup>17</sup> Other exceptions favor the defendants in drug-related litigation. The most notable exception is comment k to § 402A of the Restatement (Second) of Torts.<sup>18</sup> Comment k distinguishes some pharmaceuticals from most other manufactured products by stating that the manufacturer is not held liable for injury from drugs which are seen as unavoidably unsafe.<sup>19</sup> Use of these drugs is seen as justified, even with the apparent medical risks.<sup>20</sup> Certain products are unavoidably dangerous and are incapable of being made safe when manufactured properly. Presently, a majority of courts agree with the Restatement's view and find some drugs dangerous by nature, but it is unclear which drugs are unavoidably unsafe.<sup>21</sup>

Pharmaceuticals are treated differently by the courts than other

402A (1) (1965) provides:

One who sells any products in a defective condition unreasonably dangerous to the user or consumer or to his property is subject to liability for physical harm thereby caused . . . 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.

16. See Comment, *DES and a Proposed Theory of Enterprise Liability*, 46 *FORDHAM L. REV.* 963 (1978).

17. See *Wells v. Ortho Pharmaceutical Corp.*, 788 F.2d 741 (11th Cir. 1986), *cert. denied*, 479 U.S. 950 (1986) (A multimillion dollar settlement against the manufacturer of a spermicidal jelly without significant scientific proof of the teratogenic effects of the jelly).

18. The Restatement defines unavoidably unsafe products as 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. . . . Such a product, properly prepared, and accompanied by proper directions and warning, is not defective, nor is it *unreasonably* dangerous.

RESTATEMENT (SECOND) OF TORTS § 402A comment k (1965).

19. *Id.*

20. Comment k to §402A further provides:

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 no be 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 strictly liable 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.

*Id.*

21. See, e.g., *McElhaney v. Eli Lilly & Co.*, 575 F. Supp. 228 (D.S.D. 1983).

manufactured products.<sup>22</sup> One reason for this different treatment is the interaction which occurs between the body of the patient and the drug's chemical compound. When a drug is ingested, the response of an individual patient is difficult to predict. Every effect and each adverse reaction is unique. Frequently, the response to the chemical is more dependant on the individual's physiology than on product design. Therefore, a safely designed drug for every situation or every person may be illusory. Some commentators consider the pharmaceutical industry sufficiently unique to be categorized separately from all other forms of product liability.<sup>23</sup> Others believe the drug manufacturer should be held to the same form of strict liability as are other industries.<sup>24</sup> Still others contend that the pharmaceutical companies should be strictly liable for their products, but define the role of liability differently, usually holding manufacturers to a lesser standard.<sup>25</sup>

This article discusses strict liability as it applies to pharmaceutical manufacturers and views Halcion as an example of a potentially defective product. Part II provides a brief survey of the pharmaceutical industry, including an evaluation of the product Halcion. Part III deals with the role of government regulatory efforts. Part IV evaluates strict tort liability as it applies to the pharmaceutical industry. It also discusses manufacturing and design defects, the role of adequate warnings of potentially adverse drug reactions, causation, parties, defenses and damages. The article concludes that drug manufacturer liability should be limited for unknown and/or rare adverse reactions, and thus Upjohn should not be found liable in the *Grundberg* case.

## II. PHARMACEUTICAL BACKGROUND

### A. Drug Industry

The drug industry in America has changed dramatically since the 1930s and 1940s. Early pharmaceutical companies generally produced

22. See *infra* notes 81-82 and accompanying text.

23. See, e.g., Scott, *Medical Product and Drug Causation: How to Prove It and Defend Against It*, 56 DEF. COUNS. J. 270 (1989); Leighton, *Introduction to the Symposium on Chemical and Food Product Liability*, 41 FOOD DRUG COSM. L.J. 385 (1986); Schwartz, *Unavoidably Unsafe Products*, 42 WASH. & LEE L. REV. 1139 (1985).

24. McClellan, *Drug Induced Injury*, 25 WAYNE L. REV. 1 (1978); Maldonado, *Strict Liability and Informed Consent: 'Don't Say I Didn't Tell You So'*, 9 AKRON L. REV. 609 (1976); Merrill, *Compensation for Prescription Drug Injuries*, 59 VA. L. REV. 1 (1973); Keeton, *Products Liability—Drugs and Cosmetics*, 25 VAND. L. REV. 131 (1972).

25. Britain, *Product Honesty Is the Best Policy: A Comparison of Doctors' and Manufacturers' Duty to Disclose Drug Risks and the Importance of Consumer Expectations in Determining Product Defect*, 79 NW. U.L. REV. 342 (1984); Fink, *Education in Pharmacy and Law*, 26 J. LEGAL EDUC. 528, 538 (1974).

a complete line of medication to serve the pharmacist's needs.<sup>26</sup> These companies spent very little money on research, development, or advertisement. Customarily, the basic drug ingredients constituted seventy-five percent of corporate expenditures.<sup>27</sup>

By the time Halcion was developed in the 1980s, a major transformation had occurred within the pharmaceutical industry. The impetus for this change was the increasing efficacy of drugs.<sup>28</sup> In the early part of the century, even with hundreds of compounds on the market, few "cures" could be credited to pharmaceuticals.<sup>29</sup> Most drugs sold were for supportive care and did little to affect the course of illness directly. However, by the late 1940s and early 1950s, drugs took the offensive against disease.<sup>30</sup> Penicillin and other broad spectrum antibiotics heralded a new age, in which medicine could directly attack foreign cells without harming the host. Because most drugs are effective against only one or two conditions, hundreds of drugs are sold. In the United States, the number of physiologically active compounds number over one thousand.<sup>31</sup> These compounds in turn are mixed with other compounds which produce hundreds of thousands of products.<sup>32</sup>

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26. Many of the pharmaceutical firms are dependant on one to five of their products for the bulk of their profit. A company may produce 50 to 300 drugs but up to 50% of their profit may be produced by the one or two most profitable drugs. See Staudt, *Determining and Evaluating the Promotional Mix*, MODERN MEDICINE TOPICS 8 (July 1957).

Few products in this field have any definite assurance of future share in the market. For every 100 products introduced only 8 will be among the best prescription sellers, another 7 to 10 will pay their own way, and over 80 will fail. Up to 90% of the total company profit may be from the manufacture of the five top selling drugs. *Id.*

27. For a competent evaluation of the history of the drug industry, see E. ACKERKNECHT, *THERAPEUTICS FROM THE PRIMITIVES TO THE 20TH CENTURY* (1973).

28. Another major change that occurred in the pharmaceutical industry was the development of the transnational corporations. Global profit, rather than regional needs, would affect development, research, and marketing strategies. With these and other changes occurring, it became clear that more regulatory efforts would be needed to protect the citizenry. *Id.* at 144-45.

29. The few exceptions include Salvarsan (a cure for syphilis in Germany) in 1910, sulfonamides (antibiotics in Germany and France) in the late 1930s, and penicillin (an antibiotic in England) in the mid-1940s. *Id.* at 145.

30. Further advances in antibiotics (broad spectrum penicillins, tetracycline, erythromycin and later the cephalosporins), tranquilizers, steroids, oral contraceptives, cardiac active agents, diabetic medicines, and diuretics all were developed and first utilized in the 1950s and 1960s. *Id.* at 30.

31. The drug market is broken down into over the counter (OTC) and prescription drugs. OTCs are those that are sold directly to the consumer without the need for physician contact. The drugs within this category vary from country to country. Prescription drugs are those that require an order of a physician prior to purchase. This category makes up the largest share of the overall dollar value of drug sales worldwide. U.N. INDUSTRIAL DEVELOPMENT ORGANIZATION, *THE GROWTH OF THE PHARMACEUTICAL INDUSTRY IN DEVELOPING COUNTRIES: PROBLEMS AND PROSPECTS*, at 23, U.N. Doc. ID/204, U.N. Sales No. E.78.II.B.4 (1978).

32. While no one knows exactly how many drugs are available on the ethical drug market, it is estimated that between 10,000 and 25,000 different drugs are available for sale. Halberstrom,

Upjohn developed Halcion in the 1970s and first marketed it to Americans in 1983.<sup>33</sup> In the following six years, doctors wrote forty-three million prescriptions for the drug within the United States.<sup>34</sup>

## B. Pharmacology of Halcion

Prior to the Grundberg controversy, Halcion was the nation's most prescribed hypnotic agent.<sup>35</sup> The hypnotics (i.e., sleeping pills) are used to depress the central nervous system which causes sleep.<sup>36</sup> This form of sedative is usually reserved for mild to moderate short-term insomnia.<sup>37</sup> Benzodiazepines, such as Halcion, are considered safe and effective in the treatment of acute insomnia.<sup>38</sup>

### 1. Halcion action

Halcion is the brand name for triazolam, a short-acting hypnotic with a standard plasma half-life of two-and-one half hours.<sup>39</sup> The average patient's blood level of Halcion will peak one hour and fifteen minutes following ingestion of a single dose.<sup>40</sup> Full excretion, on the average, occurs quickly—within a range of eighty minutes to six hours.<sup>41</sup> Halcion leaves the body rapidly which prevents the "hangover" effect

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*Too Many Drugs?* F. ON MED., Mar. 1979, at 3.

33. *Woman Sues, Saying Sleeping Pill Caused Her to Shoot Mother*, Reuters, Mar. 24, 1989 (LEXIS, Nexis, Omni file); see also Arief, *Regulators Worried by Side Effects of Popular Sleeping Pill*, Reuters, Sept. 22, 1989, (LEXIS, Nexis, Omni file) (Hacion was first marketed in 1977 in Belgium). *Id.*

34. Scrip, *U.S. F.D.A. Committee—No Halcion Alarm*, WORLD PHARM. NEWS 1 (Oct. 6, 1989).

35. Sigelman, *Halcion: Waking Up to the Dangers of a Sleeping Pill*, TRIAL Nov. 1989, at 38 (1989) (Halcion is the most prescribed pharmaceutical in the America with a 46% share of the sleeping pill market in 1987). Hypnotic agents are those which are used to produce sleep. Other common drugs in this category include Dalmane and Restoril. *Id.*

36. Sleep induced by hypnotics differs from normal physiological sleep in a number of ways including reduction of REM (Rapid Eye Movement) sleep and reduction of stage IV sleep. AMERICAN MEDICAL ASSOCIATION DIVISION OF DRUGS AND TOXICOLOGY, DRUG EVALUATIONS SUBSCRIPTION, § 3, PSYCHOPHARMACOLOGIC DRUGS 1:17 (1990).

37. Chronic insomnia is treated using methods which attempt to correct the cause of the insomnia rather than using chemical depressants such as the hypnotics. Chronic insomnia is often due to physical pathology, including pain (e.g., arthritis, angina, ulcer, etc.), congestive heart failure, or respiratory disease. Other causes of insomnia may include schizophrenia, depression, anxiety, or phobias. MERCK, SHARP & DOHME RESEARCH LABORATORIES, THE MERCK MANUAL OF DIAGNOSIS AND THERAPY 1321-22 (14th ed. 1982).

38. AMERICAN MEDICAL ASSOCIATION DEPARTMENT OF DRUGS, A.M.A. DRUG EVALUATIONS 140 (4th. ed. 1980).

39. This information is available in the product insert, a copy of which is found in Appendix A.

40. E.A. Swingard, *Chapter 57: Sedatives and Hypothics*, in REMINGTON'S PHARMACEUTICAL SCIENCES 1064 (17th ed. 1985).

41. Halcion leaves the body via the urinary tract. See sample product insert in Appendix A.

often seen with other drugs.<sup>42</sup>

Most patients achieve the desired drowsiness within thirty minutes of ingestion and a full, deep sleep within one hour. Due to its excretory status (i.e., elimination from the body in most cases in less than six hours), most patients do not suffer the daytime drowsiness present with other sedatives. With its fast onset of action and its rapid rate of excretion, Halcion quickly became the sleeping pill of the 1980s for many Americans.<sup>43</sup>

Halcion assists sleep in a number of ways. It increases the speed of the onset of sleep, increases the total sleep period, and decreases the frequency of awakenings during the night. The drug's beneficial effects diminish rapidly with long-term administration. Due to this loss of efficacy, Upjohn recommends discontinuing use after one month.<sup>44</sup>

## 2. *Adverse Halcion reactions*

Adverse reactions are the unwanted interactions between a drug and a recipient's physiology. Multiple forms of adverse reactions are possible with any allergen.<sup>45</sup> Hypersensitivity<sup>46</sup> or allergic reactions,<sup>47</sup> drug interactions, excessive amounts of the desired effect, unavoidable side effects, and activation of physical illness are a few of the adverse reactions possible with any drug. Wherever possible, a manufacturer should seek to discover and eliminate these unwanted side-effects. Adverse reactions to drugs remain one of the major causes of hospitalization, illness, and death in the nation. Some authors believe that over one hundred and forty thousand deaths per year are caused by adverse drug reactions in the United States.<sup>48</sup> A product, however, that is highly beneficial to millions of patients may be deadly to a few. Most commentators agree that a prescription drug will not be considered defective if an unusually sensitive user develops an adverse reaction.<sup>49</sup>

*a. Known adverse reactions.* Pharmaceutical manufacturers are required to warn adequately of known dangers in the administration of

42. Halcion's lack of carry-over sleepiness is utilized as part of its advertisement campaign. See Prager, *An American Nightmare: Previous Suits Against Drug Companies Have Resulted in the Loss to Americans of Useful Drugs*, CORTLANDT F., 1989.

43. Sigelman, *supra* note 35, at 38 (1989).

44. PHYSICIAN'S DESK REFERENCE 2127-28 (42d ed. 1988).

45. An allergen is any foreign substance capable of eliciting an allergic or hypersensitive response. MERCK, SHARP & DOHME RESEARCH LABORATORIES, *supra* note 37, at 266.

46. Hypersensitivity is an exaggerated response to an allergen. *Id.* at 270.

47. An allergic reaction is a hypersensitivity to a allergen that builds with repeat exposure. *Id.* at 265-287.

48. TALLY & LAVENTURIER, DRUG-INDUCED ILLNESS, 229 J. A.M.A. 1043 (1974).

49. E.g., RESTATEMENT (SECOND) OF TORTS § 402A comment c (1965).



their product.<sup>50</sup> Halcion had multiple warnings of known dangers listed in the Physician Desk Reference (PDR) prior to the Grundberg incident.<sup>51</sup> Some of the dangers which had been seen in patient trials at normal dosage levels included: fetal abnormalities in pregnant women, drowsiness, dizziness, light-headedness, and impaired coordination.<sup>52</sup> Other studies report amnesia, nervousness, nausea, vomiting, tachycardia, cramps, and depression.<sup>53</sup> In addition, visual disturbances, confusional states, euphoria, diarrhea, dry mouth, nightmares, and insomnia have been noted. Upjohn also reported ringing in the ears, weakness, congestion, hepatic failure, anorexia, clouding of consciousness, slurred speech, and jaundice.<sup>54</sup> Further side-effects reported in the literature included itching, menstrual irregularities, incontinence, urinary retention, and agitation. Furthermore, spasticity, hallucinations, aggressiveness, sleepwalking, changes in libido, and death were occasionally noted.<sup>55</sup>

*b. Unknown adverse reactions.* Possibly more serious than known side-effects are those which are undiscovered prior to an adverse reaction in the ultimate consumer. While no national consensus exists on the question, some courts consider an undiscovered side-effect as a de-

50. *See, id.* at comment j (1965).

51. PHYSICIAN'S DESK REFERENCE, *supra* note 44, at 2127-28.

52. *Id.*

53. "In addition to the relatively common (ie, 1% or greater) untoward events enumerated above, the following adverse events have been reported less frequently (ie, 0.9-0.5%): euphoria, tachycardia, tiredness, confusional states/memory impairment, cramps/pain, depression, visual disturbances." *Id.* at 2128.

54. Rare (ie, less than 0.5%) adverse reactions included constipation, taste alterations, diarrhea, dry mouth, dermatitis/allergy, dreaming/nightmares, insomnia, paresthesia, tinnitus, dysesthesia, weakness, congestion, death from hepatic failure in a patient receiving diuretic drugs.

In addition to these untoward events for which estimates of incidence are available, the following adverse events have been reported in association with the use of HALCION and other benzodiazepines: amnesic symptoms (anterograde amnesia with appropriate or inappropriate behavior), confusional states (disorientation, derealization, depersonalization, and/or clouding of consciousness), dystonia, anorexia, fatigue, sedation, slurred speech, jaundice, pruritus, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention. Other factors may contribute to some of these reactions, eg, concomitant intake of alcohol or other drugs, sleep deprivation, an abnormal premorbid state, etc.

Other events reported include: paradoxical reactions such as stimulation, an agitated state (restlessness, irritability and excitation), increased muscle spasticity, sleep disturbances, hallucinations, aggressiveness, falling, somnambulism, inappropriate behavior and other adverse behavioral effects. Should these occur, use of the drug should be discontinued.

PHYSICIAN'S DESK REFERENCE, *supra* note 44, at 2128.

55. Precautions on the product insert include the following: "Some side effects reported in association with the use of HALCION appear to be dose related. These include drowsiness, dizziness, lightheadedness, and amnesia." *See* Halcion Product Insert, Appendix A.

fect and impose the same strict liability as with other defects.<sup>56</sup> Others look to comment k of § 402A and insulate drugs from standard product liability.<sup>57</sup>

### III. GOVERNMENT REGULATION OF THE PHARMACEUTICAL INDUSTRY

#### A. *History of Government Regulation*

The first attempt at government regulation of the pharmaceutical industry was the passage of the Federal (Pure) Food and Drugs Act of 1906.<sup>58</sup> The Act addressed concerns about drug safety and improper advertising practices within the industry.<sup>59</sup> For the first time, the full disclosure of a drug's composition was required.<sup>60</sup>

Congress further strengthened medication regulation by passing the Food, Drug and Cosmetic Act of 1938,<sup>61</sup> requiring proof of safety prior to marketing new drugs. Prescriptions were to be used for the majority of drugs and public access to thousands of products was to be restricted. The Food and Drug Administration (FDA) was authorized to police the market and set policy for the sale and distribution of new drugs.

Until the Kefauver-Harris Amendments to the Food, Drug and Cosmetic Act were established in 1962,<sup>62</sup> drug manufacturers were not required to prove their drug's efficacy. Due to the widespread concern of drug safety caused by the thalidomide tragedy,<sup>63</sup> the Kefauver-Harris Amendments imposed strict guidelines which led to the removal

56. See, e.g., *Brochu v. Ortho Pharmaceutical Corp.*, 642 F.2d 652 (1st Cir. 1981).

57. See, e.g., *Johnson v. American Cyanamid Co.*, 239 Kan. 279, 285, 718 P.2d 1318, 1323 (1986).

58. Ch. 3915, Pub. L. No. 59-384, 34 Stat. 768 (codified as amended in scattered sections of 21 U.S.C. (1982)). This legislation was influenced by the work of the Muckrakers. The Muckrakers were authors who believed government should protect workers from big business. One such author, Upton Sinclair, heavily influenced passage of the Federal Pure Food and Drugs Act. See generally A. CRAVEN AND W. JOHNSON, *THE UNITED STATES: EXPERIMENT IN DEMOCRACY* 519-21 (1947).

59. § 1, 34 Stat. 768 ("[I]t shall be unlawful for any person to manufacture . . . any article of food or drug which is adulterated or misbranded . . ."). See generally J. H. YOUNG, *THE TOADSTOOL MILLIONAIRES: A SOCIAL HISTORY OF PATENT MEDICINES IN AMERICA BEFORE FEDERAL REGULATION* 205-44 (1972).

60. § 8, 34 Stat. 770.

61. Ch. 675, Pub. L. 75-717, 52 Stat. 1040.

62. Drug Amendments of 1962, § 102, Pub. L. 87-781, 76 Stat. 781.

63. Thalidomide, a medication given to thousands of pregnant women in Europe, caused hundreds of severe birth defects. This drug was in the process of gaining access into the American market when the European findings were brought to the attention of the public. Sherman & Strauss, *Thalidomide: A Twenty-Five Year Perspective*, 41 *FOOD DRUG COSM. L.J.* 458, 458 (1986).

of seven thousand drugs from the market and a stricter labeling of over fifteen hundred others.<sup>64</sup>

### B. *The Current Regulatory Scheme*

Since that time, the FDA has experienced great difficulty identifying and communicating the hazards of prescription drugs.<sup>65</sup> The FDA must verify the safety and efficacy of new drugs before approving them for human use. The agency requires a lengthy experimental protocol before a drug may be marketed. Thereafter, the manufacturer must periodically review the drug's safety and efficacy in the population at large.

One of the potentially serious difficulties with the FDA's system is the agency's dependence on manufacturers for adverse reaction data. It is the manufacturer's responsibility to perform all pre-marketing tests and collect all post-marketing results. In reporting adverse reactions, drug companies have been caught falsifying tests and lying.<sup>66</sup> The most recent cases have dealt with fraud within the generic drug industry.<sup>67</sup>

Adverse reaction data collected by Upjohn led at least one foreign government to deny further marketing of Halcion.<sup>68</sup> The FDA has not placed similar restrictions on sales in the United States. Furthermore, on September 22, 1989, the FDA's Psychopharmacological Drugs Advisory Committee concluded that Halcion posed "no public health risk to patients in the U.S."<sup>69</sup> The committee, however, did recommend modifying the label to warn of the "increased incidence of anterograde amnesia compared with other hypnotics."<sup>70</sup>

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64. See Janssen, *Outline of the History of U.S. Drug Regulation*, 36 FOOD DRUG COSM. L.J. 420, 439 (1981).

65. See generally Safir, *FDA Regulations and Product Liability*, 36 FOOD DRUG COSM. L.J. 478 (1981); Ryan v. Eli Lilly & Co., 514 F. Supp. 1004 (D.S.C. 1981); Henteleff, *Interrelationships of FDA Laws and Regulations with Products Liability Issues*, 32 BUS. LAW. 1029 (1977).

66. See, e.g., Blum, *High Stakes: Wonder Drugs Are the Focus of Criminal, Civil Actions; Patients Sue Makers of Psychotropic Drugs*, Nat'l L.J., Oct. 22, 1990, at 1 (LEXIS, Nexis, Omni file). In 1985, Eli Lilly Company plead guilty to criminal charges and paid \$25,000 in fines for failing to report four deaths and six illnesses that occurred in Europe related to use of its drug, Oraflex. Eli Lilly was required to withdraw the drug from the United States market. *Id.*

67. For example, the maker of the generic form of the drug Dyazide was accused of falsifying test data and of paying bribes to FDA inspectors. Strickland & Bolar, *A Drug Company Under Siege*, N.Y. Times, Oct. 15, 1989, § 12LI, at 1, col. 3 (LEXIS, Nexis, Omni file).

68. See letter from Lawrence C. Hoff, President and Chief Operating Officer of Upjohn to John Sias, President of ABC, Inc. (Feb. 24, 1989) in Appendix B.

69. Scrip, *supra* note 34.

70. *Id.*

### 1. *Drug testing*

In the United States, bringing a new drug to the point-of-sale to the public is a long and complex process. By the time a new medicine becomes available for general use, it has been tested on both animals and humans under controlled protocol set out by the FDA.<sup>71</sup>

The FDA's protocol for testing drugs only partially shields drug manufacturers from lawsuits. The manufacturers are protected from liability for injuries only if they strictly follow FDA procedure.<sup>72</sup> Within the FDA guidelines a drug manufacturer has significant leeway in deciding the extent of product testing. Moreover, the manufacturer has almost total discretion to determine what type of experimentation and research is necessary. But in exercising this discretion, the manufacturer takes upon itself additional responsibility and increased liability exposure. For example, the duty to test is a continuing one. The manufacturer is liable if it fails to test adequately all aspects of drug usage. A drug used by consumers on a long-term basis may be deemed insufficiently tested if the only study performed was to evaluate short-term effect.<sup>73</sup>

### 2. *Reporting adverse reactions*

Continued evaluation of a product after approval by the FDA is a vital part of the regulatory process. Many pathologies become present

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71. 21 C.F.R. § 314.1 (1990). This process occurs as follows:

(1) Discovery phase: Basic research leads to the synthesis of a new chemical. This phase includes early studies of the compound's chemical properties.

(2) Pre-clinical animal testing: A short-term animal toxicity testing for evidence of safety. Tests required at this stage include pharmacodynamics, endocrinology, metabolism, toxicology, and teratology studies.

(3) Investigational New Drug (IND) filing: A request is made for authorization to begin human testing.

(4) Phase I human testing: Dosage is administered to healthy volunteers for evidence of toxicity in humans.

(5) Phase II human testing: Dosage is administered to humans with a particular pathological condition.

(6) Phase III human testing: Large-scale tests on humans are performed over a longer period to uncover unanticipated side-effects.

(7) Long-term animal studies: To determine the effects of prolonged exposures and the effects on subsequent generations.

(8) New drug application: Application for commercial marketing.

72. *Ryan v. Eli Lilly & Co.*, 514 F. Supp. 1004 (D.S.C. 1981) (Injury sustained by a manufacturer's compliance with FDA protocol shields the company from litigation). *But see Stromsodt v. Parke-Davis & Co.*, 257 F. Supp. 991 (D.N.D. 1966), *aff'd*, 411 F.2d 1390 (8th Cir. 1969) (Compliance with FDA testing protocol does not shield manufacturer from liability if adequate testing is not performed).

73. *Hoffman v. Sterling Drug*, 485 F.2d 132 (3d Cir. 1973) (Manufacturer found liable for inadequate testing of a drug which, if used over a long term, led to retinal damage).

only after years of drug use in the general population. Indeed, adverse reaction reporting has increased significantly over the past few years.<sup>74</sup> In 1985, the FDA formulated new post-marketing surveillance requirements which will better accumulate data and utilize discovered information on adverse reactions nationwide.<sup>75</sup> Manufacturers are now required to report within fifteen days any adverse drug reaction which leads to death, hospitalization, permanent disability, or need for drug therapy. Less virulent reactions must be reported "promptly," but the manufacturer is given a longer period to do so.<sup>76</sup> Manufacturers that do not comply with the reporting requirements are subject to increased liability.<sup>77</sup>

Without this government regulation, drug companies would have neither the incentive nor the ability to police their products in the market. Studies have shown that adverse reactions are grossly under-reported by the medical establishment.<sup>78</sup> The reasons for not reporting adverse reactions are numerous. First is the inability to differentiate the adverse reaction from the symptoms of disease. Second is the general reluctance of doctors and patients to report problems.<sup>79</sup> Even after a drug has been proven harmful, the physician may still not wish to report adverse reactions because of fear of malpractice liability. For example, in the mid-1960s, it was estimated that seventeen hundred deaths occurred due to the widespread use of an aerosol asthma medication. However, only six deaths were officially reported as caused by this medication.<sup>80</sup>

#### IV. STRICT LIABILITY AND PHARMACEUTICALS

##### A. *Strict Liability as Applied to Pharmaceuticals*

Most courts categorize rules of liability which apply to prescription drugs differently than rules for other products. Some courts have held that the rules of strict liability should not apply to some drugs.<sup>81</sup>

74. There were over 37,000 reports of adverse reactions in 1985. Faich, Knapp, Dreis & Turner, *National Adverse Drug Reaction Surveillance: 1985*, 257 J. A.M.A. 2068, 2068 (1987).

75. See Sills, Faich, Milstein & Turner, *Postmarketing Reporting of ADRs to FDA: An Overview of the 1985 Guideline*, 20 DRUG INFO. J. 150 (1986).

76. 21 C.F.R. § 314.80 (c)(1) (1990).

77. *Id.* at (k).

78. Faich, *Adverse Drug Experience Reporting and Product Liability*, 41 FOOD DRUG COSM. L.J. 444 (1986).

79. Merrill, *Compensation for Prescription Drug Injuries*, 59 VA. L. REV. 1, 50-68 (1973).

80. H. TEFF & C. MUNRO, *THALIDOMIDE: THE LEGAL AFTERMATH* 109 (1976).

81. See, e.g., *Johnson v. American Cyanamid Co.*, 239 Kan. 279, 285, 718 P.2d 1318, 1323 (1986) ("Orimune, the Sabin-type vaccine, is an 'apparently useful and desirable product, attended with a known but apparently reasonable risk as a matter of law.'" (quoting RESTATEMENT (SECOND) OF TORTS § 402A comment k (1965))).

Other courts apply a limited form of strict liability with less stringent rules applied to drugs. Still other courts do not differentiate between drugs and other manufactured products.<sup>82</sup>

The Restatement (Second) of Torts § 402A comment k views some drugs as "incapable of being made safe." For example, "the vaccine for the Pasteur treatment of rabies" often "leads to very serious and damaging consequences when it is injected." Such a drug is "properly prepared, and accompanied by proper directions and warning, is not defective, nor is it *unreasonably* dangerous."<sup>83</sup> Comment k does not seek to prevent all suits against drug manufacturers. While it protects drug manufacturers against liability for design defects, it does not immunize them against suits for manufacturing defects or inadequate warnings.<sup>84</sup>

One recent case supported comment k's liability limitation. In *Brown v. Superior Court*,<sup>85</sup> the California Supreme Court discussed the standards of strict liability and found that manufacturers of unavoidably unsafe drugs should not be held to this same level of responsibility. The court reasoned that subjecting a drug manufacturer to strict liability for design defects would decrease the availability of needed drugs to the public.<sup>86</sup> Even with the potential risks, the court held that all drug design defects should be protected as stated in comment k because public policy favors the development and marketing of new drugs.<sup>87</sup>

When a defective product induces property damage or physical harm in a consumer, the liability for the loss shifts to the manufacturer from the consumer. As Justice Roger J. Traynor of the California Supreme Court initially stated: "A manufacturer is strictly liable in tort when an article he places on the market, knowing that it is to be used without inspection for defects, proves to have a defect that causes injury . . . ."<sup>88</sup>

Multiple policy considerations are behind the adoption of strict liability in torts. Some of these include compensation or spreading of the loss between all consumers of a product, deterrence, encouraging useful

82. See, e.g., *Brochu v. Ortho Pharmaceutical Corp.*, 642 F.2d 652 (1st Cir. 1981) (Drug design defects should be subject to the same strict liability standards as other products).

83. RESTATEMENT (SECOND) OF TORTS § 402A comment k (1965) (emphasis in original).

84. *Id.*

85. 44 Cal. 3d 1049, 751 P.2d 470, 245 Cal. Rptr. 412 (1988).

86. *Id.* at 1063, 751 P.2d at 478, 245 Cal. Rptr. at 420.

87. *Id.* at 1064, 751 P.2d at 479, 245 Cal. Rptr. at 421.

88. See *Greenman v. Yuba Power Prod.*, 59 Cal. 2d 57, 62, 377 P.2d 897, 900, 27 Cal. Rptr. 697, 700 (1963). The California Supreme Court was the first court to adopt strict tort liability as a theory for recovery. Within one year of *Greenman*, the American Law Institute adopted RESTATEMENT (SECOND) OF TORTS § 402A (1965), which was structured along the same lines as the Traynor opinion.

conduct by both parties to an action, protecting consumer expectations, and improving the allocation of resources.<sup>89</sup>

For the rules of strict liability in tort to apply to Upjohn as the manufacturer of Halcion, the key analysis is whether the drug is and was defective. Multiple approaches have been used by the courts in the development of the concept of defectiveness.

One approach is the consumer expectation test<sup>90</sup> which weighs whether a product is unreasonably dangerous beyond that contemplated by the ordinary consumer. This test has fallen from favor in a majority of courts because it relies upon the term "unreasonable" as a requirement of defectiveness. Reasonableness is a negligence concept.<sup>91</sup> If a danger is one generally known to the ordinary consumer, then the product is not per se defective.<sup>92</sup>

Another approach is the risk/utility test.<sup>93</sup> This is a balancing test between the risk of danger associated with a product and the utility of the product to the consumer. It is the most used approach to determine defectiveness.<sup>94</sup> The emphasis is on the safety of the product rather than on the reasonable or unreasonable action of the manufacturer.<sup>95</sup> Some of the factors considered in a risk/utility analysis include the se-

89. For an excellent discussion of the policies underlying strict liability, see D. FISCHER & W. POWERS JR., *PRODUCTS LIABILITY: CASES AND MATERIALS* 50-51 (1988).

90. *RESTATEMENT (SECOND) OF TORTS* § 402A comment g (1965). Comment g provides: 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 that it left the hands of the particular seller is upon the injured plaintiff; and unless evidence can be produced which will support the conclusion that it was then defective, the burden is not sustained.

91. *RESTATEMENT (SECOND) OF TORTS* § 395 (1965). Section 395 provides: A manufacturer who fails to exercise reasonable care in the manufacturer of a chattel which, unless carefully made, he should recognize as involving an unreasonable risk of causing physical harm to those who use it for a purpose for which the manufacturer should expect it to be used . . . is subject to liability for physical harm caused to them by its lawful use. . . .

92. *Id.* at § 402A comment i (1965) (emphasis added). Comment i provides: 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.

93. *See, e.g., Boatland of Houston, Inc. v. Bailey*, 609 S.W.2d 743, 746 (Tex. 1980) (A product must be judged for defectiveness at the time of the harm and based on technology then available).

94. *See, e.g., Phillips v. Kimwood Mach. Co.*, 269 Or. 485, 525 P.2d 1033 (1974); *Dosier v. Wilcox-Crittendon Co.*, 45 Cal. App. 3d 74, 119 Cal. Rptr. 135 (1975).

95. *See Britain, supra* note 25.

verity of the risk, the likelihood of harm, the benefits of the product, and the feasibility of an alternative design.<sup>96</sup> Once a product is determined to be dangerous, the court then must balance the product's utility against its dangers. Many courts refuse to classify a drug as unreasonably dangerous if the drug's utility to mankind is viewed as greater than the potential for injury to an individual.<sup>97</sup>

Lastly, some jurisdictions offer an alternative test that utilizes a bifurcated standard: either consumer expectation or risk/utility.<sup>98</sup> Use of the disjunctive expands recovery potential for plaintiffs.<sup>99</sup>

## B. Types of Defects

Halcion can be defective in three ways. First, there could be a manufacturing defect which might cause one "batch" of the drug to deviate from the norm. Second, a design defect could exist such as a basic intrinsic flaw in the chemical design. Third, Upjohn could have provided insufficient warning of the dangers of using its sleeping pill.

### 1. Manufacturing defects

Manufacturing defects are those which deviate from the manufacturer's design or specifications and thus are different than the usual product that "comes off the assembly line."<sup>100</sup> Manufacturing defects are usually easy to identify because the products are flawed. Even though the cause of the manufacturing defect is usually negligence, difficulty in proof requires a strict liability standard, without regard to the manufacturer's reasonableness in protecting its process from error.<sup>101</sup> The consumer expectation test is utilized because the consumer expects a product to be free of defects.<sup>102</sup>

As an industry, pharmaceutical manufacturers have maintained a good record of keeping manufacturing defects to a minimum. From 1966 to 1971, 1,935 drug recalls were ordered by the FDA for mistaken labelling, contamination, adulteration, or incorrect dosage.<sup>103</sup>

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96. Wade, *On the Nature of Strict Tort Liability for Products*, 44 Miss. L.J. 825, 829 (1973) (factors to consider in a risk/utility analysis).

97. See *contra* Brochu v. Ortho Pharmaceutical Corp., 642 F.2d 652 (1st Cir. 1981).

98. *Barker v. Lull Engineering Co.*, 20 Cal. 3d 413, 573 P.2d 443, 143 Cal. Rptr. 225, (1978) (permitting the use of either the consumer expectation test or the risk/utility test).

99. D. FISCHER & W. POWERS JR., *supra* note 89, at 91.

100. *Barker v. Lull Engineering Co.*, 20 Cal. 3d 413, 429, 573 P.2d 443, 459, 143 Cal. Rptr. 225, 241 (1978).

101. D. FISCHER & W. POWERS JR., *supra* note 89, at 1.

102. See Britain, *supra* note 25.

103. M. SILVERMAN & P. LEE, *PILLS, PROFITS AND POLITICS* 333 (1974).



Apart from the sulfanilamide disaster,<sup>104</sup> there have been few episodes of death or disability due to manufacturing defects.<sup>105</sup> There have been none involving Halcion.

## 2. *Design defect*

Whereas a manufacturing defect involves an isolated deviation from the norm, a design defect involves the entire line of products. The product is manufactured according to specifications but remains unreasonably dangerous for its intended use.<sup>106</sup> Difficulty in determining design defect arises when the courts attempt to define "reasonable danger."<sup>107</sup>

If a design is found to be defective, then all of the products manufactured using that design will be defective. To determine if the initial design of Halcion was defective requires jury evaluation. The jury will be called upon to balance the utility of the drug's sedative effect against its potential adverse reactions.<sup>108</sup> The evaluation of design defect by the jury is based on a four-prong test: (1) feasibility of an alternative design (2) at the time of the manufacture which was (3) commercially available and (4) would not destroy the product's productivity.<sup>109</sup> The design of Halcion has not been shown to be defective and furthermore has been cleared by the FDA for continued use by the public.<sup>110</sup>

Some courts hold that the "FDA's decision of product marketabil-

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104. A batch of sulfanilamide was improperly mixed with a lethal solvent causing the death of many patients during the 1950s. J. Schnze, *Governmental Control of Therapeutic Drugs: Intent, Impact and Issues*, in *THE PHARMACEUTICAL INDUSTRY* 9-10 (C. Lindsay ed. 1978). For a competent evaluation of the history of the drug industry, see G. PORTER AND H. LIVESAY, *MERCHANTS AND MANUFACTURER: STUDIES IN THE CHANGING STRUCTURE OF NINETEENTH CENTURY MARKETING* (1971).

105. *Id.*

106. Comment, *Can a Prescription Drug be Defectively Designed?*: Brochu v. Ortho Pharmaceutical Corp., 31 DE PAUL L. REV. 247 (1981).

107. Birnbaum, *Unmasking the Test for Design Defect: From Negligence [to Warranty] to Strict Liability to Negligence*, 33 VAND. L. REV. 593 (1980).

108. A product is defective in design if:

(1) the plaintiff proves that the product failed to perform as safely as an ordinary consumer would expect when used in an intended and reasonably foreseeable manner, or

(2) the plaintiff proves that the product's design proximately caused injury and the defendant fails to prove . . . that on balance the benefits of the challenged design outweigh the risk of danger inherent in such design.

Barker v. Lull Engineering Co., 20 Cal. 3d 413, 426-27, 573 P.2d 443, 452, 143 Cal. Rptr. 225, 234 (1978); see also Britain, *supra* note 25, at 363-67.

109. Isaacs, *Drug Regulation, Product Liability, and the Contraceptive Crunch: Choices Are Dwindling*, 8 J. OF LEG. MED. 533 (1987) (strict liability and duty to warn).

110. Scrip, *supra* note 34.

ity disposes of the defect issue."<sup>111</sup> These courts conclude that if the FDA disapproves a product, "the product must be considered unavoidably unsafe as a matter of law and thus outside the parameters of strict liability for defective design."<sup>112</sup>

Occasionally, the government accepts responsibility for drug defects. In 1976, the government statutorily accepted liability for any adverse reactions to the swine flu immunization program.<sup>113</sup> The government took the position of the manufacturer for the purpose of liability.<sup>114</sup> This legislation was repealed in 1978.<sup>115</sup> A similar program of "no-fault" compensation was created by the National Childhood Vaccine Injury Act.<sup>116</sup> This legislation has a dual purpose. First, it allows easier access to compensation for those children who have suffered hypersensitivity reactions to vaccines.<sup>117</sup> Second, it provides liability protection for manufacturers of the vaccine to allow them to continue their production.<sup>118</sup>

### C. *Warning*

#### I. *Manufacturer's duty to warn*

Products that are both properly designed and correctly manufactured may still be dangerous and will be considered defective if not accompanied by a proper warning.<sup>119</sup> The supplier of any product, including the manufacturer of pharmaceuticals, is under a duty to use reasonable care to warn adequately about the risks associated with the use of its product.<sup>120</sup> This duty extends to the risks which the manufac-

111. See, e.g., *Collins v. Ortho Pharmaceutical Corp.*, 195 Cal. App. 3d 1539, 231 Cal. Rptr. 396 (1986) (The printed opinion is omitted in the California Appellate Reporter).

112. *Id.* 231 Cal. Rptr. at 404.

113. National Swine Flu Immunization Program of 1976, Pub. L. No. 94-380, 90 Stat. 1113; see also *Ducharme v. Merrill-Nat'l Labs.*, 574 F.2d 1307 (5th Cir.), *cert. denied*, 439 U.S. 1002 (1978).

114. 90 Stat. 1116.

115. Health and Services Amendments of 1978, Pub. L. 95-626, 92 Stat. 3551.

116. Pub. L. 99-660, 100 Stat. 3755 (codified at 42 U.S.C. §§ 300aa-1 to -33 (1986)).

117. 100 Stat. 3758 (codified at 42 U.S.C. § 300aa-10 (1988)).

118. 100 Stat. 3758-59 (codified at 42 U.S.C. §300aa-11 (1988)).

119. See, e.g., *Basko v. Sterling Drug*, 416 F.2d 417, 426 (2d Cir. 1969). ("[T]here is no strict liability . . . unless the consumer first establishes a breach of the manufacturer's duty to warn . . . by showing either (1) that the manufacturer did not warn of a known danger, or (2) that the manufacturer gave inadequate warnings."); see also *Jacobson v. Colorado Fuel & Iron Corp.* 409 F.2d 1263, 1271 (9th Cir. 1969).

120. The Restatement (Second) of Torts defines this knowledge requirement as follows:

(1) The words "reason to know" are used throughout the Restatement . . . to denote the fact that the actor has information from which a person of reasonable intelligence or of the superior intelligence of the actor would infer that the fact in question exists, or that such person would govern his conduct upon the assumption that such fact

turer actually knows of and to those which, through reasonable care, it should have known.<sup>121</sup>

The duty of a pharmaceutical manufacturer to warn arises when the product is known to cause a particular side effect. The manufacturer is not responsible for unforeseeable or unknown dangers it is unable to discover with reasonable care.<sup>122</sup> Nor is the company a guarantor of the safety of a product which causes an unusual hypersensitivity reaction if that reaction was not known to be a side-effect of the product.<sup>123</sup>

The "unavoidably dangerous" protection afforded prescription drugs under Restatement (Second) of Torts § 402A comment k is available, unless the manufacturer has provided an adequate warning of potential adverse reactions.<sup>124</sup> The protection is not available to those manufacturers who have failed to follow FDA guidelines for testing and marketing of their product.<sup>125</sup>

Drugs are an exception to the rule requiring a warning of danger to the ultimate consumer.<sup>126</sup> The drug manufacturer's duty to warn includes a warning to physicians of the special risks that accompany normal use.<sup>127</sup> In the majority of cases, there is no duty to warn the patient directly.<sup>128</sup> For the sake of pharmaceutical warnings, the physician is considered the "learned intermediary"<sup>129</sup> and as such the duty to

exists.

(2) The words "should know" are used throughout the Restatement . . . to denote the fact that a person of reasonable prudence and intelligence or of the superior intelligence of the actor would ascertain the fact in question in the performance of his duty to another, or would govern his conduct upon the assumption that such fact exists.

RESTATEMENT (SECOND) OF TORTS § 12 (1965).

121. See *e.g.*, *Lindsay v. Ortho Pharmaceutical Corp.*, 637 F.2d 87 (2d Cir. 1980); *Sterling Drug, Inc., v. Cornish*, 370 F.2d 82 (8th Cir. 1966); *Incollingo v. Ewing*, 444 Pa. 263, 282 A.2d 206 (1971), *rev'd on other grounds*, 491 Pa. 561, 421 A.2d 79 (1977)

122. *Griggs v. Combe, Inc.*, 456 So. 2d 790 (Ala. 1984); *Freeman v. United States*, 704 F.2d 154 (5th Cir. 1983).

123. *Gravis v. Parke, Davis & Co.*, 502 S.W. 2d 863 (Tex. Civ. App. 1973).

124. *Davila v. Bodelson*, 103 N.M. 243, 704 P.2d 1119 (App. 1985).

125. *Id.*

126. See, *e.g.*, *Buckner v. Allergan Pharmaceuticals*, 400 So. 2d 820 (Fla. Dist. Ct. App. 1981); *Lindsay v. Ortho Pharmaceutical Corp.*, 637 F.2d 87 (2d Cir. 1980). "[T]he manufacturer's duty is to warn the doctor, not the patient. The doctor acts as an 'informed intermediary' between the manufacturer and the patient, evaluating the patient's needs, assessing the risks and benefits of available drugs, prescribing one, and supervising its use." *Id.* at 91.

127. See, *e.g.*, *Fellows v. USV Pharmaceutical Corp.*, 502 F. Supp. 297 (D. Md. 1980) (The manufacturer has a duty to provide warnings to physician but the duty does not extend to the patient); *Ezagui v. Dow Chemical Corp.*, 598 F.2d 727 (2d Cir. 1979).

128. See, *e.g.*, *Fellows*, 502 F. Supp. at 297.

129. In *Reyes v. Wyeth Laboratories*, 498 F.2d 1264 (5th Cir.), *cert. denied*, 419 U.S. 1096 (1974), the court gives an excellent definition of the learned intermediary doctrine.

[W]here prescription drugs are concerned, the manufacturer's duty to warn is limited to

warn, in most instances, ends when an adequate effort is made by the company to instruct physicians of the drug's potential side-effects.<sup>130</sup> The pharmaceutical manufacturer has no obligation to warn the ultimate user of dangerous propensities "where there is an intermediary who is not a mere conduit of the product, but rather administers it on an individual basis."<sup>131</sup> After the manufacturer gives the physician the necessary information, it is then the duty of the doctor to warn the patient.<sup>132</sup> Halcion's warnings are provided to the prescribing physicians. It is their duty, not Upjohn's, to pass the information on to the patient.

The manufacturer's duty to warn does not end with the purchase of the drug by the patient. Post-sale warnings are also required. The manufacturer is considered an expert in regards to its product.<sup>133</sup> As an expert, the manufacturer has the duty to stay abreast of the scientific data in the field and the further duty to warn physicians of potential harm caused by the product.<sup>134</sup>

Should an unknown hazard be discovered after the drug has been sold, the manufacturer is required to make reasonable efforts to inform the consumer.<sup>135</sup> This requirement is usually satisfied with warnings to physicians in the form of "Dear Doctor" letters<sup>136</sup> or via detail persons. One court has said that "[a]lthough a product be reasonably safe when manufactured . . . risks thereafter revealed by user operation and brought to the attention of the manufacturer or vendor may impose upon one or both a duty to warn."<sup>137</sup>

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an obligation to advise the prescribing physician of any potential dangers that may result from the drug's use . . . . As a medical expert, the prescribing physician can take into account the propensities of the drug, as well as the benefits of any medication against its potential dangers . . . . Pharmaceutical companies . . . in selling prescription drugs are required to warn only the prescribing physician, who acts as a "learned intermediary" between manufacturer and consumer.

*Id.* at 1276 (5th Cir. 1974).

130. See *Leesley v. West*, 165 Ill. App. 3d 135, 518 N.E.2d 758 (App. Ct.), *appeal denied*, 119 Ill. 2d 558, 522 N.E.2d 1246 (1988); *Stone v. Smith, Kline & French Laboratories*, 447 So. 2d. 1301 (Ala. 1984); *Mauldin v. Upjohn Co.*, 697 F.2d 644 (5th Cir. 1983).

131. *Bacardi v. Holzman*, 182 N.J. Super. 422, 424, 442 A.2d 617, 618 (1981) (The learned intermediary doctrine protects a prescription drug manufacturer even where the manufacturer knew that the physician might not warn the patient).

132. See *Crain v. Allison*, 443 A.2d 558, 562 (D.C. App. 1982); *Salis v. United States*, 522 F. Supp. 989, 1000 (M.D. Pa. 1981).

133. *Barson v. E.R. Squibb & Sons*, 682 P.2d 832 (Utah 1984).

134. *Id.* at 834 (citing *McEwen v. Ortho Pharmaceutical Corp.*, 270 Or. 375, 528 P.2d 522 (1974)) (actual or constructive knowledge is required).

135. *Schenebeck v. Sterling Drug*, 423 F.2d 919 (8th Cir. 1970).

136. See Appendix C for an example of a "Dear Doctor" letter.

137. *Cover v. Cohen*, 61 N.Y.2d 261, 268, 461 N.E.2d 864, 871, 473 N.Y.S.2d 378, 385 (1984) (citations omitted).

One such drug was Aralan. Initial testing did not show any significant side-effects. However, after use by the general public, evidence of irreversible blindness in a number of patients was brought to the attention of the manufacturer. The drug manufacturer gave a minimum amount of credence to this information and chose not to disseminate these findings to the medical community. The courts repeatedly have held that the manufacturer was liable because it failed to warn the public adequately after a side-effect became known.<sup>138</sup>

After the Grundberg homicide, the newly discovered side-effects of Halcion were brought to the attention of Upjohn. Upjohn was required to warn every licensed physician and pharmacist in the nation of the previously unknown danger.

The manufacturer is responsible for performing studies of its product when adverse reactions are reported. The results of these studies, if adverse to the product, must be reported to the public (i.e., doctors).<sup>139</sup> This duty to report new adverse findings extends to more than the research of the manufacturer and includes all industry knowledge (i.e., state of the art). Constructive knowledge of potential side effects is presumed with the publication of articles in scientific journals which relate to the product.<sup>140</sup> A number of these articles concerning Halcion were published soon after the Grundberg incident. This scientific data assisted Upjohn in formulating a new adequate warning of its product.<sup>141</sup>

In *Lindsay v. Ortho Pharmaceutical Corp.*,<sup>142</sup> the court explained that the duty to warn "is a continuous one, requiring the manufacturer to keep abreast of the current state of knowledge of its product as gained through research, adverse reaction reports, scientific literature, and other available methods."<sup>143</sup> Various unsuccessful attempts to legislate a post-sale warning requirement include the proposed Federal Products Liability Act.<sup>144</sup>

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138. *Sterling Drug v. Yarrow*, 408 F.2d 978, 987 (8th Cir. 1969) (manufacturer held liable for failing to warn of a known side effect); *Sterling Drug v. Cornish*, 370 F.2d 82, 85 (8th Cir. 1966).

139. *See Schenebeck v. Sterling Drug*, 423 F.2d 919 (8th Cir. 1970); *O'Hare v. Merck & Co.*, 381 F.2d 286 (8th Cir. 1967).

140. *Feldman v. Lederle Laboratories*, 97 N.J. 429, 479 A.2d 374 (1984); *see also Gilhooly, Learned Intermediaries, Prescription Drugs, and Patient Information*, 30 ST. LOUIS L.J. 633 (1986).

141. *See Scrip, supra* note 34, at 1.

142. 637 F.2d 87 (2d Cir. 1980).

143. *Id.* at 92.

144. Product Liability Act, § 44, 99th Cong., 2d Sess. (1984). The following standard was proposed: "[T]he manufacturer may be responsible for failure to warn if, after the product was made, the manufacturer discovered or should have discovered the danger which caused the claimant's harm and failed to provide post-manufacture warnings to the claimant as a reasonably pru-

While the duty of drug manufacturers to provide warnings usually only extends to the physician,<sup>145</sup> in cases where the manufacturer knows that the product will reach the public without individualized medical intervention, the drug manufacturer must also warn the public at large.<sup>146</sup> Such an example is immunizations, where everyone is given a standardized dose of the vaccine without individualized dosing by the physician.<sup>147</sup> Likewise, birth control pills are given out without much individual attention. Therefore, no protection exists for the drug producer under the learned intermediary rule in situations where the manufacturer had actual or constructive knowledge of the potential for the public to acquire the product without significant physician intervention.<sup>148</sup> Halcion does not fall into this category because direct physician contact is required before a patient has access to the drug.

## 2. Adequacy of warning

Adequacy of the warning is a major issue in determining reasonableness. If the warning is adequate, then the defendant drug producer will usually prevail, even if the product is unavoidably unsafe.<sup>149</sup> Adequacy of the warning is achieved when it is obviously displayed, when it gives a fair appraisal of the extent of the danger, and when it properly instructs the user in how to use the product.<sup>150</sup> Likewise, a warning is adequate when it "warns with the degree of intensity demanded by the nature of the risk."<sup>151</sup> A warning, however, may be inadequate if it is "unduly delayed, reluctant in tone or lacking in a sense of ur-

dent person would have done." *Id.*

145. See *Brochu v. Ortho Pharmaceutical Corp.*, 642 F.2d 652 (1st Cir. 1981); *Dyer v. Best Pharmacal*, 118 Ariz. 465, 577 P.2d 1084 (Ct. App. 1978).

146. This is the standard in vaccines and mass immunizations. See *Reyes v. Wyeth Laboratories*, 498 F.2d 1264 (5th Cir.), *cert. denied*, 419 U.S. 1096 (1974); *Davis v. Wyeth Laboratories*, 399 F.2d 121 (9th Cir. 1968).

147. *Brazzell v. United States*, 788 F.2d 1352 (8th Cir. 1986).

148. *Williams v. Lederle Laboratories*, 591 F. Supp. 381 (S.D. Ohio 1984).

149. *Formella v. Ciba-Geigy Corp.*, 100 Mich. App. 649, 300 N.W.2d 356 (1980).

150. Madden, *The Duty to Warn in Products Liability: Contours and Criticism*, 89 W. Va. L. REV. 221, 310-20 (1987); *Richards v. Upjohn Co.*, 95 N.M. 675, 679, 625 P.2d 1192, 1196 (Ct. App. 1980). To be considered adequate:

1. the warning must adequately indicate the scope of the danger;
2. the warning must reasonably communicate the extent or seriousness of the harm that could result from misuse of the drug;
3. the physical aspects of the warning must be adequate to alert a reasonably prudent person to the danger;
4. a simple directive warning may be inadequate when it fails to indicate the consequences that might result from failing to follow it; and . . .
5. the means to convey the warning must be adequate.

*Id.*

151. *Seley v. G.D. Searle & Co.*, 67 Ohio St. 2d 192, 198, 423 N.E.2d 831, 837 (1981).

gency."<sup>152</sup> Prior to *Grundberg*, Halcion's package insert warned of the potential for serious side effects including in "[r]are (i.e., less than 0.5%) [cases] death from hepatic failure."<sup>153</sup> Whether or not this type of warning was adequate is a question for the jury to decide.

Even if an adequate warning is given of the risk, it will not insulate the manufacturer from liability when a cure for the defect could have been accomplished with little effort. The court in *Brochu v. Ortho Pharmaceutical Corp.* found that "when an unreasonable danger could have been eliminated without excessive cost or loss of product efficiency, liability may attach even though . . . there was adequate warning."<sup>154</sup> Moreover, the value of an adequate warning may be diminished by statements which lead the user to minimize the importance of the warning. For example, a warning of one manufacturer concerning birth control pills contained studies showing an increased incidence of thrombosis in British women. The court held that having a study dealing with British women did little to amplify concern of thrombosis in American women and therefore did not adequately warn this group.<sup>155</sup>

In addition, most courts require warnings to be given if an allergic reaction may affect a substantial number of people.<sup>156</sup> Some courts have required a duty to warn of rare adverse reactions if the end result would be exceedingly serious.<sup>157</sup> The Restatement (Second) of Torts states that "[w]here . . . the product contains an ingredient to which a substantial number of the population are allergic . . . the seller is required to give warning . . . and a product bearing such a warning, which is safe for use if it is followed, is not in defective condition, nor is it unreasonably dangerous."<sup>158</sup>

### 3. *Methods of warning*

Warnings may be satisfied in a number of ways. Labeling, package inserts, advertising, and interaction with drug company detail persons may all act as adequate warnings to decrease liability.

*a. Labeling.* The FDA has numerous requirements for the label-

152. *Id.*

153. See the copy of the package insert found within Appendix A.

154. 642 F.2d 652, 655 (1st Cir. 1981) (quoting *Thibault v. Sears, Roebuck & Co.*, 118 N.H. 802, 808, 395 A.2d 843, 847 (1978)).

155. *McEwen v. Ortho Pharmaceutical Corp.*, 570 Or. 375, 528 P.2d 522 (1974).

156. *Kaempfe v. Lehn & Fink Prods. Corp.*, 21 A.D.2d 197, 249 N.Y.S.2d 840 (App. Div. 1964), *aff'd*, 20 N.Y.2d 818, 231 N.E.2d 294, 284 N.Y.S.2d 818 (1967).

157. *Tomer v. American Home Prod. Corp.*, 170 Conn. 681, 368 A.2d 35 (1976); *Crocker v. Winthrop Laboratories*, 514 S.W.2d 429 (Tex. 1974) (Drug manufacturers must properly warn of rare adverse reactions if they may be severe).

158. RESTATEMENT (SECOND) OF TORTS § 402A (1965).

ing of pharmaceuticals.<sup>159</sup> These are minimum requirements only and do not relieve the manufacturer of its duty to fully warn of dangers for which it has actual or constructive knowledge.<sup>160</sup> The basic labeling regulation as promulgated by the FDA is that all material facts relating to the drug are to be presented on the package.<sup>161</sup>

An FDA special advisory committee on September 22, 1989, unanimously recommended the agency change Halcion's label to advise doctors that the drug may be more likely to cause amnesia than similar medications.<sup>162</sup> The committee further recommended that the FDA revise the labels of all hypnotic benzodiazepines.<sup>163</sup> Their major concern was to warn of "traveler's amnesia," a condition that occasionally occurs when a person takes a long-acting sleeping pill to sleep a relatively short period of time.<sup>164</sup>

*b. Package inserts.* The package insert is the method developed by the FDA for instructing physicians and patients about the make-up, side-effects, indications, and dosing of the product.<sup>165</sup> The most important feature of the package insert is the requirement that the information contained therein is completely based on substantial evidence. No "hype" or promotion is permitted to be included. Because physicians have almost unlimited access to drug information through a variety of sources, the package insert is not intended to be the most current repository of information concerning the benefits of a drug. Instead, it has the purpose of informing the physician of any substantial evidence that has been found relating to the drug's benefits or side-effects.<sup>166</sup>

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159. 21 C.F.R. § 201 (1990).

160. *Feldman v. Lederle Laboratories*, 97 N.J. 429, 479 A.2d 374 (1984).

161. 21 C.F.R. § 201.5-.10 (1990) ("Labeling of a . . . drug . . . shall be deemed to be misleading if it fails to reveal facts that are . . . material.").

162. *Sleeping Pill Not Serious Health Threat*, United Press Int'l, Sept. 23, 1989 (LEXIS, Nexis, Omni file).

163. Benzodiazepines are replacing barbiturates as the most prescribed sedatives. Various benzodiazepines show a great difference in their side-effect profile. The major side-effects within this family of drugs include drowsiness, fatigue, and ataxia. More significant but less common side-effects include: Rage, hostility, paranoia, hallucinations, depression, insomnia, nightmares, and anterograde amnesia. *Drugs That Cause Psychiatric Symptoms*, 31 MEDICAL LETTER 114 (1989).

164. See *Sleeping Pill Not Serious Health Threat*, *supra* note 162.

165. *Pharmaceutical Mfr. Ass'n v. Food & Drug Admin.*, 484 F. Supp. 1179 (D. Del. 1980).

166. The court in *Pharmaceutical Manufacturers Ass'n* stated that Congress intended patients using prescription drugs, as well as those using over-the-counter drugs, to receive 'facts material with respect to consequences which may result from the use . . .' When it is determined that the possible side effects of a drug when used as customarily prescribed are sufficiently serious as to be material to the patient's decision on use of the drug, [the FDA] may require disclosure of those side effects on the labeling.



The package insert contains information based on data submitted to the FDA by the manufacturer dealing with the safety and efficacy of the drug.<sup>167</sup> A physician is not required to follow the instructions of the package insert. If the doctor chooses not to do so, he or she may be concerned about increased liability.<sup>168</sup> This fear leads many physicians to practice cookbook medicine (i.e., following the product insert instructions implicitly without regard to the patient's individual reactions). However, in general, most physicians are not the dispenser of drugs and so they do not see the product inserts, which can be problematic. Likewise, while pharmacists have access to inserts, they usually rely on computer data for the majority of their product information.

Some courts construe a manufacturer's failure to comply with rules requiring package inserts as constituting negligence per se.<sup>169</sup> Other courts have held that failure to follow statutory regulation concerning inserts is not a controlling issue.<sup>170</sup> Within Halcion's package insert, Upjohn has always included the information required by the FDA. The most recent change occurred after the Grundberg incident. At that time, Upjohn discontinued the 0.5 mg dosage and added a warning of "traveler's amnesia" and "anterograde amnesia" to Halcion's package insert.<sup>171</sup>

*c. Advertising.* Emphasis on product promotion is one of the more controversial actions of the pharmaceutical industry. Manufacturers spend over one-fourth of gross income from drug sales on marketing.<sup>172</sup> The majority of this money is spent on advertising and detail persons. The Pharmaceutical Manufacturers Association, realizing the importance of this issue, has promulgated the *Code of Fair Practices in the Promotion of Drug Products*.<sup>173</sup> But, as with many such professional ethical codes, the written word is often overlooked for an improved bottom line.

Drug manufacturers are the dominant, if not the only, source of information about drug risks and benefits for most prescribing physicians. Other independent sources of information, such as medical jour-

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*Id.* at 1186.

167. 21 C.F.R. § 201.5 (1990).

168. *Ohligschlager v. Proctor Community Hosp.*, 55 Ill. 2d 411, 303 N.E.2d 392 (1973) (The court held that the physician's deviation from the package insert constituted negligence.).

169. *Lukaszewicz v. Ortho Pharmaceutical Corp.*, 510 F. Supp. 961, *amended*, 532 F. Supp. 211 (E.D. Wis. 1981).

170. *See MacDonald v. Ortho Pharmaceutical Corp.*, 394 Mass. 131, 475 N.E.2d 65 (1985), *cert. denied*, 474 U.S. 920 (1985).

171. *See Scrip*, *supra* note 34, at 1.

172. Harrell, *Pharmaceutical Marketing*, in *THE PHARMACEUTICAL INDUSTRY* 80 (C. Lindsay ed. 1978).

173. *See* Appendix D.

nals, may be reluctant to publish research criticizing products of drug manufacturers because drug advertising makes up the largest share of medical journal revenue.<sup>174</sup>

Courts have held drug manufacturers liable for advertisements which dilute proper warnings or reduce reliance of the physician on a package insert.<sup>175</sup> For example, Parke-Davis, the manufacturer of chloramphenicol, provided warnings in its package insert on the dangers of aplastic anemia with use of the drug. The California Supreme Court found that Parke-Davis had diluted the effect of the warning to such a degree, through advertising and promotional schemes, that it caused doctors to disregard the package insert.<sup>176</sup> Courts have held that a company incurs liability if it causes a prescribing physician to disregard the warnings that are mandated by the FDA.<sup>177</sup> Some courts have held the manufacturer liable, even when the physician acted in a negligent manner, if the physician's actions were induced through over-promotion.<sup>178</sup>

Drug manufacturers may be held to a warranty standard based on advertising.<sup>179</sup> Drug manufacturers rarely expose themselves to liability by expressly warranting their products.<sup>180</sup> Instead, exposure to breach of warranty liability most often arises through implied warranty and misrepresentation.<sup>181</sup> In its advertisements, Upjohn has always asserted

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174. See S. GREENBERG, *THE QUALITY OF MERCY* 267-83 (1971).

175. *Love v. Wolf*, 226 Cal. App. 2d 378, 38 Cal. Rptr. 183 (1964). The court stated: [I]f such over-prescription by the doctor was not caused by the over-promotion of Parke-Davis, then, however negligent such over-promotion may have been, Parke-Davis could not be held liable. Its negligence would not have been an inducing, or proximate, cause of the resulting injuries. Dr. Wolf's negligence would have been an intervening, independent, and solely proximate cause . . . .

On the other hand, if the over-promotion can reasonably be said to have induced the doctor to disregard the warnings previously given, the warning given is thereby withdrawn or cancelled, and if, furthermore, the jury could have found that the doctor here actually prescribed the drug to cure an infection for which the company's advertising or its detail men could actually have recommended its use, then the pharmaceutical company's negligence remains as an inducing cause coinciding with the negligence of the doctor to produce the result.

*Wolf*, 226 Cal. App. at 399-400, 38 Cal. Rptr. at 196 (citation omitted).

176. *Id.*

177. See *Toole v. Richardson-Merrell, Inc.*, 251 Cal. App. 2d 689, 60 Cal. Rptr. 398 (1967).

178. See, e.g., *Stevens v. Parke, Davis & Co.*, 9 Cal. 3d. 51, 507 P.2d 653, 107 Cal. Rptr. 45 (1973).

179. *Id.*

180. *But see Spiegel v. Saks* 34th Street, 43 Misc. 2d 1065, 252 N.Y.S.2d 852 (Sup. Ct. 1964), *aff'd*, 26 A.D.2d 660, 272 N.Y.S. 972 (1966) (A product advertised as absolutely safe is subject to litigation for breach of express warranty).

181. An implied warranty may be breached when a manufacturer fails to warn adequately of known dangers. See *supra* notes 115-116 and accompanying text.

Halcion's rapidity of action, fast elimination, and daytime alertness.<sup>182</sup> Since the Grundberg incident, Upjohn has emphasized the safety of the product.<sup>183</sup>

*d. Detail persons.* Detail persons, the sales representatives of ethical drugs, occupy a position different than that of other sales persons. Their potential misrepresentation of the product, rather than being harmless fluff, may lead to death or disfigurement of the ultimate consumer. Detail persons, acting as liaison between physicians and manufacturer, are the most common transmitters of new information concerning pharmaceuticals. The pharmaceutical industry employs almost 40,000 detail persons.<sup>184</sup>

Detail persons are frequently torn between a desire to increase the substantial profits of the drug manufacturer<sup>185</sup> and a duty to inform the physician of product side-effects and possible contra-indications. Great potential exists for detail persons to mislead physicians in order to increase sales. Manufacturers are vicariously liable for the actions of the detail persons which are within the scope of their employment.<sup>186</sup> Some courts have held that the liability extends even beyond the scope of employment.<sup>187</sup>

An otherwise adequate warning provided by the company can be nullified by an overzealous detail person. High pressure sales by intense, occasionally knowledgeable, detail persons often determine physician-use patterns. Even though the oral communications of detail persons are difficult to monitor as to completeness or accuracy, drug companies cannot escape liability for improper over-promotion of safety by detail persons.<sup>188</sup>

If the detail person convinces the doctor to disregard warnings provided by the manufacturer, the company may be held liable as the cause of the injury.<sup>189</sup> At least one court has held that detail persons

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182. For examples of Halcion advertisements, see Prager, *supra* note 42.

183. *Id.*

184. PHARMACEUTICAL MANUFACTURERS ASSOCIATION, *PRESCRIPTION DRUG INDUSTRY FACT BOOK* 56 (1986).

185. See generally J. LIDSTONE, *MARKETING PLANNING FOR THE PHARMACEUTICAL INDUSTRY* (1987); R. NORRIS, *PILLS PESTICIDES AND PROFITS* (1982).

186. RESTATEMENT (SECOND) OF AGENCY § 229 (1958).

187. See, e.g., Schering Corp. v. Cotlow, 94 Ariz. 365, 385 P.2d 234 (1963).

188. Most physicians tolerate visits and direct sale attempts by detail persons in order to acquire samples of medications. Detail persons frequently use tactics of peer pressure ("all the doctors in this area are using my drug"), bribery ("if you do a study on 200 of your patients using my drug, then the company will award you an honorarium of a trip to Europe to continue your research"), and humiliation ("chiropractors are the only people still suggesting using the other medication") to push their product. Survey of doctors at MacDonald Health Center, Brigham Young University, March 1990 (on file at the BYU Journal of Public Law office).

189. Stevens v. Parke-Davis & Co., 9 Cal. 3d. 51, 107 Cal. Rptr. 45, 507 P.2d 653 (1973)

have a duty to warn of potential adverse reactions.<sup>190</sup> Liability is possible because the doctor might otherwise have been aware of the risks that were involved had the detail persons given adequate warning.<sup>191</sup>

#### D. Causation

As in negligence actions, causation must be proved in strict tort liability. Professor Prosser states that "[s]trict liability eliminates both privity and negligence; but it still does not prove the plaintiff's case."<sup>192</sup> The standard elements of proof, as enumerated in § 402A of the Restatement (Second) of Torts, are: first, proof that the product was defective; second, proof that the defect existed at the time it left the control of the defendant; third, proof that the defect created a product that was unreasonably dangerous for the intended or foreseeable use; and, fourth, proof that the defect caused the injury.<sup>193</sup> Within the pharmaceutical industry, the most common ways to prove causation are epidemiological and statistical studies, expert testimony, direct or circumstantial evidence, or a combination of these methods.<sup>194</sup>

In situations where the plaintiff is unable to identify the defective product's specific manufacturer, an industry-wide liability has been devised.<sup>195</sup> Liability may be imposed on every manufacturer of a generic product. It is then the responsibility of the various defendants to prove they did not supply the defective product.<sup>196</sup> Industry-wide liability,

(An active sales program, led by a detail person, convinced a doctor to disregard the package insert warnings); *Toole v. Richardson-Merrell, Inc.*, 251 Cal. App. 2d 689, 709, 60 Cal. Rptr. 398, 413-14 (1967) (Company did not warn of known adverse reactions).

190. *Incollingo v. Ewing*, 444 Pa. 263, 289, 282 A.2d 206, 220 (1971), *rev'd on other grounds*, 491 Pa. 561, 421 A.2d 1027 (1977):

We think that whether or not the warnings on the cartons, labels and literature of Parke, Davis in use in the relevant years were adequate, and whether or not the printed words of warning were in effect cancelled out and rendered meaningless in the light of the sales effort made by the detail men, were questions properly for the jury. Action designed to stimulate the use of a potentially dangerous product must be considered in testing the adequacy of a warning as to when and how the product should not be used; if detail men are an effective means of selling a product and explaining its nature, a jury could find that they also afforded an effective medium of conveying a warning.

191. *See, e.g., Schenebeck v. Sterling Drug*, 423 F.2d 919 (8th Cir. 1970); *Krug v. Sterling Drug, Inc.*, 416 S.W.2d 143 (Mo. 1967).

192. Prosser, *The Fall of the Citadel (Strict Liability to the Consumer)*, 50 MINN. L. REV. 791, 840 (1966).

193. RESTATEMENT (SECOND) OF TORTS § 402A (1965).

194. Middlekauff, *The Current Law Regarding Toxic Torts: Implications for the Food Industry*, 41 FOOD DRUG COSM. L.J. 387, 404-05 (1986).

195. Comment, *Industry Wide Liability*, 13 SUFFOLK U.L. REV. 980 (1979); *Mulcahy v. Eli Lilly & Co.*, 386 N.W.2d 67 (Iowa 1986) (DES market share liability).

196. Comment, *The Market Share Theory: Sindell's Contribution to Industry Wide Liability*, 19 HOU. L. REV. 107 (1982).

however, is not an issue in *Grundberg* since Upjohn is the sole producer of Halcion.

Since the product is destroyed by ingestion at the time of injury, it is difficult to prove a drug was manufactured defectively. This difficulty is amplified because the plaintiff must prove that the drug was defective at the time it left the control of the manufacturer and that the defect was present at the time of injury.<sup>197</sup> On the other hand, a design defect is easier to prove because all of the same type of drugs are equally defective and available for testing. In a failure to warn case, the plaintiff must prove that lack of proper warning was the proximate cause of the injury. The failure to warn must be the direct link between the product and the injury. The plaintiff must further show the manufacturer either knew or should have known the danger of harm from the drug.<sup>198</sup>

Defendant liability may be severed by the introduction of an intervening cause. In strict liability litigation, courts appear very willing to view intervening causes as being unforeseeable.<sup>199</sup>

Most courts view the terms "user" and "consumer" liberally. Historically, privity was required before permitting recovery. Today, a user may be far removed from the initial privity of contract.<sup>200</sup> If it is foreseeable that a person will be a user, then that person is a potential plaintiff.<sup>201</sup>

It is not necessary to prove that Halcion was the only cause of the injury, only that it was one of the causes. If, for example, the patient were to ingest multiple drugs, then each drug might be viewed as a cause-in-fact of the subsequent harm. At least one court has held a manufacturer of one defective drug liable for the entire injury sustained by the ingestion of multiple drugs.<sup>202</sup>

The foreseeability of the harm caused by a product is an issue in many courts.<sup>203</sup> If it is not foreseeable that Mrs. Grundberg would shoot her mother, then this is not the type of injury that would induce liability. Some courts now reject the foreseeability of the harm ap-

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197. RESTATEMENT (SECOND) OF TORTS § 402A.

198. *Id.*

199. See generally D. FISCHER & W. POWERS JR., *supra* note 89, at 409-11.

200. RESTATEMENT (SECOND) OF TORTS § 402A comment 1 (1965). Comment 1 provides: He may be a member of the family of the final purchaser, or his employee, or a guest at his table, or a mere donee from the purchaser. The liability stated is one in tort, and does not require any contractual relation, or privity of contract, between the plaintiff and the defendant.

201. *Winnett v. Winnett*, 57 Ill. 2d 7, 310 N.E.2d 1 (1974).

202. *Basko v. Sterling Drug*, 416 F.2d 417 (2d Cir. 1969).

203. *Helene Curtis Indus. v. Pruitt*, 385 F.2d 841, 859-64 (5th Cir. 1967); *Bigbee v. Pacific Tel. & Tel. Co.*, 34 Cal. 3d 49, 665 P.2d 947, 192 Cal. Rptr. 857 (1983).

proach and instead look to the foreseeability of the use.<sup>204</sup>

### *E. Physician and/or Pharmacist Liability*

It is unfortunate that many physicians and pharmacists are ignorant of the potential side-effects associated with the drugs they prescribe. One study revealed that under thirteen percent of drug use was evaluated as rational, twenty-one-and-one-half percent was considered questionable, and amazingly over sixty-five percent was judged irrational.<sup>205</sup> Because of the prevalence of drugs in the treatment of patients, it is conceivable that every malpractice case could have a pharmaceutical component.

The application of traditional liability rules to pharmaceutical manufacturers is problematic. For example, the defined consumer of prescription drugs is the physician, not the patient. The patient has little input into the drug selected by the physicians. The physician holds a position as a "learned intermediary" and as such takes upon himself some of the manufacturer's liability even in the case of product defect.<sup>206</sup> The physician who prescribed Halcion to Mrs. Grundberg could be liable for all side-effects he or she should have known if he failed to warn the patient adequately.

Physicians and pharmacists who find themselves in a suit resulting from a defective product have some recourse.<sup>207</sup> There is a potential tort action against the manufacturers of the defective products for both the injury to the patient and for damage to reputation and earnings.<sup>208</sup> In many circumstances, this leads to plaintiffs playing one potential defendant against another.<sup>209</sup>

204. See e.g., *Baker v. International Harvester Co.*, 660 S.W.2d 21 (Mo. Ct. App. 1983).

205. M. SILVERMAN & P. LEE, *supra* note 103, at 289-90.

206. Comment, *Strict Tort Liability/Negligence/ Prescription Drugs: A Pharmaceutical Company Owes No Duty to a Non-Patient Third Party to Warn Doctors or Hospitals of the Side Effects of a Drug and a Hospital or Doctor Owes No Duty to a Non-Patient Third Party to Warn a Patient of the Effects of a Prescription Drug*, 77 ILL. B.J. 227 (1988); Comment, *Torts—Duty to Warn—Incorrect Prescription of Unavoidably Unsafe Drugs*, 22 KAN. L. REV. 281 (1984).

207. See Merrill, *Compensation for Prescription Drug Injuries*, 59 VA. L. REV. 1, 50-68 (1973).

208. See, e.g., *Oksenholt v. Lederle Laboratories*, 294 Or. 213, 656 P.2d 293 (1982); Mobilia, *Allergic Reactions to Prescription Drugs: A Proposal for Compensation*, 48 ALB. L. REV. 343, 364-65 (1984).

209. See Willig, *Physicians, Pharmacists, Pharmaceutical Manufacturers: Partners in Patient Care, Partners in Litigation?*, 37 MERCER L. REV. 755 (1986).

## F. *Defenses*

Defenses to strict products liability differ from one jurisdiction to the next. In Utah, Upjohn has three potential defenses: assumption of the risk, comparative fault, and misuse.

### 1. *Assumption of the risk*

The Restatement (Second) of Torts describes assumption of the risk as "the form of contributory negligence which consists of voluntary and unreasonable encounter of a known danger."<sup>210</sup> If the consumer knew of the product's defect but disregarded the danger and used the product, he or she is barred from seeking to recover against the defendant. The defendant must prove that the plaintiff knew and understood the danger and that the plaintiff "voluntarily and unreasonably" consented to being exposed to it.<sup>211</sup>

Assumption of the risk is an essential concept for pharmaceutical litigation defense. If adequate warning is given to the doctor and the doctor disregards these dangers, then the physician/patient has assumed some of the risk for potential adverse reactions. Since creating Halcion, Upjohn has maintained a warning against certain uses of its product. One such warning suggested discontinuing use of the drug after one month and warned of the chance for increased side-effects with long term use. By prescribing the drug over a longer period of time, the physician/patient may have assumed the risk of increased side-effects.

### 2. *Comparative fault*

Comparative fault measures the plaintiff's fault in comparison to the manufacturer's fault and places upon each a percentage value. Most states that have comparative negligence systems have applied a comparative fault scheme to strict tort liability litigation.<sup>212</sup> For negligence actions in Utah, a statutory "49/51" comparative fault system exists.<sup>213</sup> In this system, if the plaintiff is more than half at fault, no recovery is permitted. This is not the case in strict tort liability where a "pure" comparative fault system exists.<sup>214</sup> In a pure system, a plaintiff may recover the percent of damage caused by the defendant, regardless of the fault attributable to the plaintiff.<sup>215</sup>

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210. RESTATEMENT (SECOND) OF TORTS § 402A comment n (1965).

211. *Smith v. Clayton & Lambert Mfg. Co.*, 488 F.2d 1345, 1349 (10th Cir. 1973).

212. *Daly v. General Motors Corp.*, 20 Cal. 3d 725, 575 P.2d 1162, 144 Cal. Rptr. 380 (1978).

213. *Mulherin v. Ingersoll-Rand Co.*, 628 P.2d 1301, 1303-04 (Utah 1981).

214. *Id.*

215. *Id.*

The goal of strict tort liability is not to create in the manufacturer an insurer for product-induced injuries. Comparative fault provides more equity in allocating risks and preventing manufacturers and other consumers from sharing in the costs attributable to those who fail to use products carefully. Most courts which have permitted a comparative fault defense have also permitted defenses of assumption of the risk and misuse.<sup>216</sup> The jury is usually instructed to combine the percentage from each of these defenses and give the percentage of fault as the sum of the three.<sup>217</sup>

If Halcion were shown to have a particular defect, Mrs. Grundberg would be able to recover for the percentage of damage induced by the defect. The total damage would be calculated, and the percentage of fault she caused would be deducted from the award.

### 3. *Product misuse*

The defense of product misuse is permitted when the plaintiff has used a product for a purpose not reasonably foreseeable to the manufacturer.<sup>218</sup> The Restatement (Second) of Torts recognizes the defense of product misuse. Comment h of § 402A provides: "If the injury results from abnormal handling . . . the seller is not liable."<sup>219</sup> The defense of misuse may be utilized if the plaintiff's misuse of the product was a contributing cause of the injury.<sup>220</sup>

To use this defense, the plaintiff's misuse of the product must be unforeseeable.<sup>221</sup> The definition of unforeseeable is the important issue. Taking four times the standard dosage of a medication may be foreseeable, but five times may be unforeseeable. There is no standard, fixed, arbitrary cutoff. It is left for the fact finder to determine foreseeability on a case-by-case basis.

216. See generally Fischer, *Products Liability—Applicability of Comparative Negligence to Misuse and Assumption of the Risk*, 43 MO. L. REV. 643 (1978).

217. See, e.g., *Duncan v. Cessna Aircraft Co.*, 665 S.W.2d 414 (Tex. 1984).

218. *Perfection Paint & Color Co. v. Konduris*, 147 Ind. App. 106, 107, 258 N.E.2d 681, 682 (1970).

219. RESTATEMENT (SECOND) OF TORTS § 402A comment h (1965). Comment h provides:

A product is not in a defective condition when it is safe for normal handling and consumption. If the injury results from abnormal handling, as where a bottled beverage is knocked against a radiator to remove the cap, or from abnormal preparation for use, as where too much salt is added to food, or from abnormal consumption, as where a child eats too much candy and is made ill, the seller is not liable. Where, however, he has reason to anticipate that danger may result from a particular use, as where a drug is sold which is safe only in limited doses, he may be required to give adequate warning of the danger (see Comment j), and a product sold without such warning is in a defective condition.

220. *Mulherin v. Ingersoll-Rand Co.*, 628 P.2d 1301, 1302 (Utah 1981).

221. *Id.*



Upjohn claims that Mrs. Grundberg misused Halcion by taking it longer than was suggested in the product insert and in higher doses than was intended by the manufacturer.<sup>222</sup> If Upjohn can prove these allegations to the jury, then the defense of misuse will restrict her recovery.

### G. Damages

Similar to negligence litigation, strict liability provides for property and personal damage recovery.<sup>223</sup> With both negligence and strict liability, damage is part of a prima facie case.<sup>224</sup> Mrs. Grundberg and her mother's estate seek six million dollars in general damages and fifteen million dollars in punitive damages.<sup>225</sup>

Commentators have differed in their views of punitive damage awards in strict liability litigation. Some assert that punitive damage awards should be granted as punishment for wanton, willful, reckless, malicious, or "outrageous conduct."<sup>226</sup> Other jurisdictions grant punitive damage awards as a form of deterrence to others who might commit the same outrageous conduct.<sup>227</sup> Most jurisdictions use punitive damages for any combination of the above reasons.<sup>228</sup>

Punitive damage awards are common in strict liability litigation involving pharmaceutical products.<sup>229</sup> The plaintiff has the burden of proving the defendant's outrageous conduct by "clear and convincing proof."<sup>230</sup> Punitive damage awards serve to punish inappropriate manufacturing practices and to stop "product suppliers from making eco-

222. This information is contained in a letter from Lawrence C. Hoff, President and Chief Operating Officer of Upjohn to John Sias, President of ABC, Inc. The letter was sent in response to the "20/20" broadcast of Feb. 17, 1989, which dealt with the Grundberg incident. A copy of the letter is found in Appendix B.

223. See RESTATEMENT (SECOND) OF TORTS § 402A (1965).

224. A prima facie case of negligence requires a duty owed by the defendant to the plaintiff, breach of that duty, causation, and damages. See generally W. PROSSER, LAW OF TORTS § 96 (4th ed. 1971).

225. See Prager, *supra* note 42.

226. See RESTATEMENT (SECOND) OF TORTS § 908(2) (1965). Section 908(2) provides:

Punitive damages may be awarded for conduct that is outrageous, because of the defendant's evil motive or his reckless indifference to the rights of others. In assessing punitive damages, the trier of fact can properly consider the character of the defendant's act, the nature and extent of the harm to the plaintiff that the defendant caused or intended to cause and the wealth of the defendant.

227. See, e.g., *Malcolm v. Little*, 295 A.2d 711 (Del. 1972).

228. See, e.g., *Miller v. Watkins*, 200 Mont. 455, 653 P.2d 126 (1982); *Newton v. Standard Fire Ins. Co.*, 291 N.C. 105, 229 S.E.2d 297 (1976); see also W. KEETON, D. DOBBS, R. KEETON & D. OWEN, PROSSER AND KEETON ON TORTS, § 2, at 9 (5th ed. 1984).

229. See *Hoffman v. Sterling Drug*, 485 F.2d 132, 144-47 (3d Cir. 1973).

230. *Acosta v. Honda Motor Co.*, 717 F.2d 828, 833 (3d Cir. 1983).

nostic decisions, not to remedy the defects of the product."<sup>231</sup> The most common type of drug cases in which punitive damages are granted are where the manufacturer had knowledge of adverse reactions but failed to properly warn of the danger.<sup>232</sup>

## V. CONCLUSION

The public should be free to purchase goods without fear of defect. Strict tort liability is a valid means to insure that products function without injury. On the other hand, it is unreasonable for all products to be totally safe and risk free for consumers. A knife with a dull blade might be safer than with a sharp blade, but part of the sharp knife's efficacy is due to the very cause of its dangerous propensity, namely its sharpened edge. Ice cream would be safer without the heavy cholesterol content but the joy in eating it comes from its richness which clogs our arteries. Medication is unique because it is ingested into the body with the knowledge that in a certain number of individuals there will be serious side-effects. This is just as true for over-the-counter medications, such as aspirin or Tylenol, as it is for prescription-strength medication, such as Halcion.

It is true that drugs can be made safer, but, even so, certain idiosyncratic reactions will occur which will cause a few to suffer. The answer for those few individuals might be for the government or the manufacturer to set up a trust fund for such reactions which could be drawn upon when a severe reaction occurs. Rather than hamper the medical establishment with increased liability, the courts should take the forefront in the fight to provide a strong defense for drug manufacturers.

Prior to *Grundberg*, Upjohn gave a proper warning for the potential dangers of Halcion. The majority of possible adverse reactions to Halcion were discussed in that warning. Unless it can be shown that Upjohn was not diligent in testing the drug, the manufacturer should not be held responsible for an unknown reaction, no matter how serious the consequences.

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231. *Neal v. Carey Canadian Mines*, 548 F. Supp. 357 (E.D. Pa. 1982), *aff'd*, *Van Buskirk v. Carey Canadian Mines*, 791 F.2d 30 (3rd Cir. 1986).

232. *See G.D. Searle & Co. v. Superior Court*, 49 Cal. App. 3d 22, 122 Cal Rptr. 218 (1975); *Roginsky v. Richardson-Merrell, Inc.*, 378 F.2d 832 (2d Cir. 1967); *Toole v. Richardson-Merrell, Inc.*, 251 Cal. App. 2d 689, 60 Cal. Rptr. 398 (1967).

## APPENDIX A

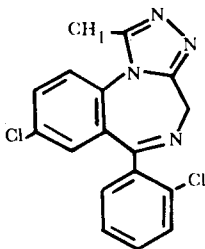
## DESCRIPTION

HALCION Tablets contain triazolam, a triazokobenzodiazepine hypnotic agent.

Triazolam is a white crystalline powder, soluble in alcohol and poorly soluble in water. It has a *molecular weight* of 343.21.

The chemical name for *triazolam* is 8-chloro-6-(*o*-chlorophenyl)-1-methyl-4H-s-triazolo-[4,3-*u*][1,4] benzodiazepine.

The structural formula is represented below:



Each HALCION tablet, for oral administration, contains 0.125 mg. or 0.25 mg. of triazolam. Inactive ingredients 0.125 mg.-cellulose, corn starch, docusate sodium, FD&C red no. 3, FD&C blue no 2 lactose magnesium stearate sodium benzoate. 0.25 mg.-cellulose, corn starch, docusate sodium, FD&C blue no 2, lactose, magnesium stearate, silicon dioxide, sodium benzoate.

## CLINICAL PHARMACOLOGY

Triazolam is a hypnotic with a short mean plasma half-life reported to be in the range of 1.5 to 5.5 hours. In normal subjects treated for seven days with four times the recommended dose, there was no evidence of altered systemic bioavailability, rate of elimination, or accumulation. Peak plasma levels are reached within 2 hours following oral administration. Following recommended doses of HALCION, triazolam peak plasma levels in the range of 1 to 6 ng/ml are seen. The plasma levels achieved are proportional to the dose given.

Triazolam and its metabolites, principally as conjugated glucuronides which are presumably inactive, are excreted primarily in the urine. Only small amounts of unmetabolized triazolam appear in the urine. The two primary metabolites accounted for 79.9% of urinary excretion. Urinary excretion appeared to be biphasic in its time course.

HALCION Tablets 0.5 mg. in two separate studies, did not affect the prothrombin times or plasma warfarin levels in male volunteers administered sodium warfarin orally.

Extremely high concentrations of triazolam do not displace bilirubin bound to human serum albumin *in vitro*.

Triazolam <sup>14</sup>C was administered orally to pregnant mice. Drug-related material appeared uniformly distributed in the fetus with <sup>14</sup>C concentrations approximately the same as in the brain of the mother.

In sleep laboratory studies, HALCION Tablets significantly decreased sleep latency, increased the duration of sleep and decreased the number of nocturnal awakenings. After two weeks of consecutive nightly administration, the drug's effect on total wake time is decreased, and the values recorded in the last third of the night approach baseline levels. On the first and/or second night after drug discontinuance (first or second post-drug night), total time asleep, percentage of time spent sleeping, and rapidity of falling asleep frequently were significantly less than on baseline (pre-drug) nights. This effect is often called "rebound" insomnia.

The type and duration of hypnotic effects and the profile of unwanted effects during administration of benzodiazepine drugs may be influenced by the biologic half-life of administered drug and any active metabolites formed. When half-lives are long, drug or metabolites may accumulate during periods of nightly administration and be associated with impairments of cognitive and mo-

tor performance during waking hours, the possibility of interaction with other psychoactive drugs or alcohol will be enhanced. In contrast, if half-lives are short, drug and metabolites will be cleared before the next dose is ingested, and carry-over effects related to excessive sedation or CNS depression should be minimal or absent. However, during nightly use for an extended period, pharmacodynamic tolerance or adaptation to some effects of benzodiazepine hypnotics may develop. If the drug has a short half-life of elimination, it is possible that a relative deficiency of the drug or its active metabolites (ie, in relationship to the receptor site) may occur at some point in the interval between each night's use. This sequence of events may account for two clinical findings reported to occur after several weeks of nightly use of rapidly eliminated benzodiazepine hypnotics: 1) increased wakefulness during the last third of the night, and 2) the appearance of increased signs of day-time anxiety reported by one author in a selected group of patients.

#### INDICATIONS AND USAGE

HALCION Tablets contain triazolam which is a hypnotic agent useful in the short-term management of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings.

In polysomnographic studies in man of 1 to 42 days duration, triazolam decreased sleep latency, increased duration of sleep, and decreased the number of nocturnal awakenings.

It is recommended that HALCION not be prescribed in quantities exceeding a one-month supply.

#### CONTRAINDICATIONS

HALCION Tablets are contraindicated in patients with known hypersensitivity to this drug or other benzodiazepines.

Benzodiazepines may cause fetal damage when administered during pregnancy. An increased risk of congenital malformations associated with the use of diazepam and chlordiazepoxide during the first trimester of pregnancy has been suggested in several studies. Transplacental distribution has resulted in neonatal CNS depression following the ingestion of therapeutic doses of a benzodiazepine hypnotic during the last weeks of pregnancy.

HALCION is contraindicated in pregnant women. If there is a likelihood of the patient becoming pregnant while receiving HALCION she should be warned of the potential risk to the fetus. Patients should be instructed to discontinue the drug prior to becoming pregnant. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered.

#### WARNINGS

Overdosage may occur at four times the maximum recommended therapeutic dose (See DOSAGE & ADMINISTRATION). Patients should be cautioned *not* to exceed prescribed dosage.

Because of its depressant CNS effects, patients receiving triazolam should be cautioned against engaging in hazardous occupations requiring complete mental alertness such as operating machinery or driving a motor vehicle. For the same reason, patients should be cautioned about the simultaneous ingestion of alcohol and other CNS depressant drugs during treatment with HALCION Tablets.

As with some but not all benzodiazepines, anterograde amnesia of varying severity and paradoxical reactions have been reported following therapeutic doses of HALCION.

#### PRECAUTIONS

**General:** In elderly and/or debilitated patients, it is recommended that treatment with HALCION Tablets be initiated at 0.125 mg. to decrease the possibility of development of oversedation, dizziness, or impaired coordination.

Some side effects reported in association with the use of HALCION appear to be dose related. These include drowsiness, dizziness, lightheadedness, and amnesia.

The relationship between dose and what may be more serious behavioral phenomena is less certain. Specifically, some evidence, based on spontaneous marketing reports, suggests that confusion, bizarre or abnormal behavior, agitation and hallucinations may also be dose related, but this evidence is inconclusive. In accordance with good medical practice it is recommended that therapy be initiated at the lowest effective dose (See DOSAGE AND ADMINISTRATION).

Caution should be exercised if HALCION is prescribed to patients with signs or symptoms of depression which could be intensified by hypnotic drugs. Suicidal tendencies may be present in such patients and protective measures may be required. Intentional overdosage is more common in these patients, and the least amount of drug that is feasible should be available to the patient at any one time.

The usual precautions should be observed in patients with impaired renal or hepatic function and chronic pulmonary insufficiency.

**Information for Patients:** To assure safe and effective use of HALCION, the following information and instructions should be given to patients.

1. Inform your physician about any alcohol consumption and medicine you are taking now, including drugs you may buy without a prescription. Alcohol should generally not be used during treatment with hypnotics.
2. Inform your physician if you are planning to become pregnant, if you are pregnant, or if you become pregnant while you are taking this medicine.
3. Inform your physician if you are nursing.
4. Until you experience how this medication affects you, do not drive a car or operate potentially dangerous machinery, etc.
5. Do *not* increase prescribed dosage.
6. Patients should also be advised that they may experience an increase in sleep complaints (rebound insomnia) on the first night or two after discontinuing the drug.

**Laboratory Tests:** Laboratory tests are not ordinarily required in otherwise healthy patients.

**Drug Interactions:** Both pharmacodynamic and pharmacokinetic interactions have been reported with benzodiazepines. In particular, triazolam produces additive CNS depressant effects when co-administered with other psychotropic medications, anticonvulsants, antihistamines, ethanol, and other drugs which themselves produce CNS depression.

Pharmacokinetic interactions can occur when triazolam is administered along with drugs that interfere with its metabolism. Specific examples, documented with evidence from controlled trials, show that the co-administration of either cimetidine or erythromycin with triazolam cause an approximate doubling of the elimination half-life and plasma levels of triazolam. Consequently, consideration of dose reduction may be appropriate in patients treated concomitantly with either cimetidine or erythromycin and triazolam.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** No evidence of carcinogenic potential was observed in mice during a 24-month study with HALCION in doses up to 4000 times the human dose.

**Pregnancy:**

1. Teratogenic Effects: Pregnancy Category X. See CONTRAINDICATIONS.
2. Non-Teratogenic Effects: It is to be considered that the child born of a mother who is on benzodiazepines may be at some risk for withdrawal symptoms from the drug, during the postnatal period. Also, neonatal flaccidity has been reported in an infant born of a mother who had been receiving benzodiazepines.

**Nursing Mothers:** Human studies have not been performed, however, studies in rats have indicated that HALCION and its metabolites are secreted in milk. Therefore, administration of HALCION to nursing mothers is not recommended.

**Pediatric Use:** Safety and efficacy of HALCION in children below the age of 18 have not been established.

**ADVERSE REACTIONS**

During placebo-controlled clinical studies in which 1003 patients received HALCION Tablets, the most troublesome side effects were extensions of the pharmacologic activity of triazolam, eg. drowsiness, dizziness, or lightheadedness.

The figures cited below are estimates of untoward clinical event incidence among subjects who participated in the relatively short duration (ie. 1 to 42 days) placebo-controlled clinical trials

of HALCION. The figures cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors often differ from those in clinical trials. These figures cannot be compared with those obtained from other clinical studies involving related drug products and placebo as each group of drug trials are conducted under a different set of conditions.

Comparison of the cited figures, however, can provide the prescriber with some basis for estimating the relative contributions of drug and non-drug factors to the untoward event incidence rate in the population studied. Even this use must be approached cautiously, as a drug may relieve a symptom in one patient while inducing it in others. [For example, an anticholinergic, anxiolytic drug may relieve dry mouth (a sign of anxiety) in some subjects but induce it (an untoward event) in others.]

	<u>HALCION</u>	<u>Placebo</u>
Number of Patients	1003	997
% Patients Reporting:		
<u>Central Nervous System</u>		
Drowsiness	14.0	6.4
Headache	9.7	8.4
Dizziness	7.8	3.1
Nervousness	5.2	4.5
Lightheadedness	4.9	0.9
Coordination Disorders/Alaxia	4.6	0.8
<u>Gastrointestinal</u>		
Nausea/Vomiting	4.6	3.7

In addition to the relatively common (ie, 1% or greater) untoward events enumerated above, the following adverse events have been reported less frequently (ie, 0.9-0.5%), euphoria, tachycardia, tiredness, confusional states/memory impairment, cramps/pain, depression, visual disturbances.

Rare (ie, less than 0.5%) adverse reactions included constipation, taste alterations, diarrhea, dry mouth, dermatitis/allergy, dreaming/nightmares, insomnia, paresthesia, tinnitus, dyesthesia, weakness, congestion, death from hepatic failure in a patient also receiving diuretic drugs.

In addition to these untoward events for which estimates of incidence are available, the following adverse events have been reported in association with the use of HALCION and other benzodiazepines; amnesic symptoms (anterograde amnesia with appropriate or inappropriate behavior), confusional states (disorientation, derealization, depersonalization, and/or clouding of consciousness), dystonia, anorexia, fatigue, sedation, slurred speech, jaundice, pruritus, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention. Other factors may contribute to some of these reactions, eg, concomitant intake of alcohol or other drugs, sleep deprivation, an abnormal premorbid state, etc.

Other events reported include, paradoxical reactions such as stimulation, an agitational state (restlessness, irritability and excitation), increased muscle spasticity, sleep disturbances, hallucinations, aggressiveness, falling, somnambulism, inappropriate behavior and other adverse behavioral effects. Should these occur, use of the drug should be discontinued.

Laboratory analyses were performed on all patients participating in the clinical program for HALCION. The following incidences of abnormalities were observed in patients receiving HALCION and the corresponding placebo group. None of these changes were considered to be of physiological significance.

Number of Patients % of Patients Reporting	HALCION 380		Placebo 361	
	Low	High	Low	High
<u>Hematology</u>				
Hematocrit	•	•	•	•
Hemoglobin	•	•	•	•
Total WBC Count	1.7	2.1	•	1.3
Neutrophil Count	1.5	1.5	3.3	1.0
Lymphocyte Count	2.3	4.0	3.1	3.8
Monocyte Count	3.6	•	4.4	1.5
Eosinophil Count	10.2	3.2	9.8	3.4
Basophil Count	1.7	2.1	•	1.8
<u>Urinalysis</u>				
Albumin	—	1.1	—	•
Sugar	—	•	—	•
RBC/HPF	—	2.9	—	2.9
WBC/HPF	—	11.7	—	7.9
<u>Blood Chemistry</u>				
Creatinine	2.4	1.9	3.6	1.5
Bilirubin	•	1.5	1.0	•
SGOT	•	5.3	•	4.5
Alkaline Phosphatase	•	2.2	•	2.6

\*Less than 1%

When treatment with HALCION is protracted, periodic blood counts, urinalysis and blood chemistry analyses are advisable.

Minor changes in EEG patterns, usually low-voltage fast activity have been observed in patients during therapy with HALCION and are of no known significance.

#### DRUG ABUSE AND DEPENDENCE

**Controlled Substance:** Triazolam is a controlled substance under the Controlled Substance Act and HALCION Tablets have been assigned to Schedule IV.

**Abuse and Dependence:** Withdrawal symptoms similar in character to those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepine drugs. These can range from mild dysphoria to a major syndrome which may include abdominal and muscle cramps, vomiting, sweating, tremor, and convulsions.

Patients with a history of seizures should not be abruptly withdrawn from any CNS depressant agent, including HALCION. Addiction-prone individuals, such as drug addicts and alcoholics, should be under careful surveillance when receiving triazolam because of the predisposition of such patients to habituation and dependence. As with all hypnotics, repeat prescriptions should be limited to those who are under medical supervision.

#### OVERDOSAGE

Because of the potency of triazolam, overdosage may occur at 2 mg. four times the maximum recommended therapeutic dose (0.5 mg).

Manifestations of overdosage with HALCION Tablets include somnolence, confusion, impaired coordination, slurred speech, and, ultimately, coma. As in all cases of drug overdosage, respiration, pulse, and blood pressure should be monitored and supported by general measures when necessary. Immediate gastric lavage should be performed. An adequate airway should be maintained. Intravenous fluids may be administered.

Experiments in animals have indicated that cardiopulmonary collapse can occur with massive intravenous doses of triazolam (over 100 mg/kg. more than 10,000 times the maximum daily

human dose). This could be reversed with positive mechanical respiration and the intravenous infusion of norepinephrine bitartrate or metaraminol bitartrate. Hemodialysis and forced diuresis are probably of little value. As with the management of intentional overdosage with any drug, the physician should bear in mind that multiple agents may have been ingested by the patient.

The oral LD<sub>50</sub> in mice is greater than 1000 mg/kg and in rats is greater than 5000 mg/kg.

#### **DOSAGE AND ADMINISTRATION**

It is important to individualize the dosage of HALCION Tablets for maximum beneficial effect and to help avoid significant adverse effects.

The recommended dose for most adults is 0.25 mg before retiring. A dose of 0.125 mg may be found to be sufficient for selected patients. A dose of 0.5 mg should be reserved for those patients who do not respond adequately to a lower dose since the risk of several adverse reactions increases with the size of the dose administered.

In geriatric and/or debilitated patients, the recommended dosage range is 0.125 mg to 0.25 mg. Therapy should be initiated at 0.125 mg in this group.

As with all medications, the lowest effective dose should be used.

#### **HOW SUPPLIED**

HALCION Tablets are available in the following strengths and package sizes:

0.125 mg (pale lavender):

Bottles of 100

NDC 0009-0010-01

Unit Dose Pkg. (100)

NDC 0009-0010-22

VISIPAK® Reverse Numbered Pack (100)

NDC 0009-0010-04

Bottles of 500

NDC 0009-0010-11

0.25 mg (powder blue, scored)

Bottles of 100

NDC 0009-0017-01

Unit Dose Pkg (100)

NDC 0009-0017-08

VISIPAK Reverse Numbered Pack (100)

NDC 0009-0017-17

Bottles of 500

NDC 0009-0017-02

Store at controlled room temperature 15°-30° C (59°-86° F).

Caution: Federal law prohibits dispensing without prescription.

US Patent No. 3,987,052

**The Upjohn Company**  
**Kalamazoo, Michigan 49001, USA**

Revised April 1989

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## APPENDIX B

## THE UPJOHN COMPANY

7000 PORTAGE ROAD  
KALAMAZOO MICHIGAN 49001-0199 U.S.A.

LAWRENCE C. HOFF  
President and Chief  
Operating Officer  
TELEPHONE 1616/323-6127

February 24, 1989

John Sias, President  
Capital Cities/ABC, Inc.  
1330 Avenue of the Americas  
New York, New York 10019

Dear Mr. Sias:

As president and chief operating officer of the The Upjohn Company, I am responding to the February 17 broadcast of a segment of "20/20" that concerned HALCION Tablets, an Upjohn product. After careful medical, scientific and legal analysis of the broadcast, it is our opinion that the segment on Halcion was misleading and contained unfounded allegations and substantial misrepresentations. My intent in writing is to clarify our concerns.

"20/20" focused a large segment of the broadcast on the case of Mrs. Jo Grundberg of Utah. From our analysis of "20/20" and related newspaper clippings, Mrs. Grundberg was not following the package insert recommendations. The reporter, Stone Phillips, clearly stated that not only was Mrs. Grundberg using the drug to excess, but she also was taking it nearly every night for fourteen months, both of which are considered inappropriate use. However, "20/20" concluded in its broadcast that Halcion was to blame for the murder of Mrs. Grundberg's mother. "... (H)ad it not been for the Halcion, she would not have killed her mother." This is simply not true. "20/20" made no mention of Mrs. Grundberg's medical history or her concomitant use of other medications. However, in other media reports of her case it was clearly indicated that she was also taking diazepam and was suffering from depression. The package insert states "caution should be exercised if Halcion is prescribed to patients with signs or symptoms of depression which could be intensified by hypnotic drugs." The package insert also cautions against the simultaneous ingestion of other psychotropic medications.

Furthermore, "20/20" misrepresented the ruling in the Grundberg case which was not that Halcion caused her to do what she did, but that her judgment was impaired at the time of her mother's murder for a variety of reasons. To ignore these other reasons and focus on Halcion alone, concluding it was the "real" reason for the criminal activity is irresponsible and does a great disservice to the millions of patients and their physicians who have successfully used Halcion.

John Sias, President  
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The second anecdotal experience focused on was the case of Steve McCoy. Upon close examination of the records included in your story, it appears there were some discrepancies between the visual and verbal accounts of McCoy's situation. Namely, a psychological evaluation on May 1, 1987 reportedly gave McCoy a clean bill of health immediately prior to his taking Halcion. The "20/20" report stated that a year after using Halcion he was diagnosed as suffering from a major depression with psychosis. Yet, the date on the admittance form presented during the broadcast shows McCoy's diagnosis of depression with psychosis appearing to be August 26, 1987. This obviously is not one year after the original diagnosis of his mental health status and it also falls before the stock market crash in October 1987, which "20/20" capitalized on and dramatically recreated in its broadcast.

The extensive warnings on Halcion claimed by "20/20" to be required by the Food and Drug Administration were inaccurate. Nowhere in the package insert does it state that therapy should be no longer than 14 days. The label's actual wording is, "it is recommended that Halcion not be prescribed in quantities exceeding a one-month supply." Because Halcion is indicated for short-term or transient insomnia, Upjohn includes this recommendation to physicians to encourage patient reevaluation on a periodic basis to determine if the medication is still needed.

"20/20" seemed to try to sensationalize the fact that depression, anxiety and memory loss have been reported with the use of Halcion, when the reality is that these side effects have been reported with benzodiazepines in general. It must also be noted that such side effects are unusual, occurring in less than 1 percent of patients in controlled clinical trials.

The package insert for Halcion states that "the recommended dose for most adults is 0.25 mg before retiring....A dose of 0.5 mg should be reserved for those patients who do not respond adequately to a lower dose since the risk of several adverse reactions increases with the size of the dose administered. In geriatric and/or debilitated patients, the recommended dosage range is 0.125 mg to 0.25 mg. Therapy should be initiated at 0.125 mg in this group." While the majority of patients are effectively treated with the 0.25 mg dose, some patients because of size, age and other factors are not responsive to this dosage strength and require 0.5 mg. While the 0.5 mg tablet is no longer produced, the dosage strength remains a valuable option for therapy-resistant patients. You claim that recommending the 0.5 mg dosage is "defeating the whole purpose of removing the .5 mg tablets in the first place." The Upjohn Company disagrees. The purpose for discontinuing the 0.5 mg tablet strength was an additional effort to emphasize usage of the lowest effective dose and as a result of the worldwide trend toward decreased prescribing and usage of the 0.5 mg tablet.

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The discontinuation of the 0.5 mg tablet is consistent with medical evidence developed over a number of years regarding the use of Halcion and other benzodiazepines: 1.) therapy should be initiated at the lowest effective dose and 2.) some adverse events may be dose related. Side effects of the benzodiazepines that are related to their pharmacologic activity, e.g. drowsiness, lightheadedness, amnesia and dizziness, are dose related. The relationship of dose with the risk of other adverse reactions is less obvious. By emphasizing the lower dosages of Halcion, introducing a 0.125 tablet strength and revising the product labeling to reflect a starting dose of 0.25 mg, Upjohn continues to encourage the safest dose possible while maintaining efficacy. However, Upjohn maintains that tailoring the dosage to the individual is essential, and for those patients that do not respond to 0.25 mg, the 0.5 mg dosage remains an important therapeutic option.

Of utmost concern to me was a statement that Upjohn refused to speak with "20/20." This is patently untrue. We did decline to provide an on-camera interview, but we spoke long and often with your producer, providing a great deal of background information and offering additional assistance during several phone conversations. We also provided a written statement to "20/20." Refusing to speak implies total silence and carries an undesirable implication that clearly misrepresents Upjohn's position, which is that the entertainment program "20/20" was far more interested in sensationalizing the anecdotal reports of a few, selected individuals rather than providing a balanced story based on medical and scientific fact.

Dr. Martin Scharf, a known opponent of Halcion, stated that he has "had instances of people who have either attempted murder or literally committed murder claiming to be under the influence of the medication." The key phrase is "claiming to be under the influence" of Halcion. By using the word "claiming," no verification is established whether or not the drug was actually involved, and by stating the individual was "under the influence" provides no clear causal relationship. Also, no clarification was made whether or not those persons were also under the influence of alcohol, had a history of depression or psychotic behavior or whether other medications were involved. In other words, the viewers only saw part of the picture.

As reporter Stone Phillips dramatically fanned a computer printout of adverse reactions on screen and claimed they were related to Halcion, no mention was made that the FDA explicitly states that such voluntary reports cannot be used to estimate incidence of adverse reactions. The FDA letter that accompanies the printout of spontaneously reported data states: "The information contained in the reports is considered raw information and has not been verified as to a cause and effect relationship. This information cannot be used to estimate the incidence of adverse drug reactions." There are numerous factors affecting the Spontaneous Reporting System of the FDA's Division of Drug and Biological Produce Experience. Among them are the reporting practices of each manufacturer. This is particularly significant because approximately 80 percent of such reports come to the system directly from manufacturers. Most of the triazolam reports in the FDA data base originated with The Upjohn

John Sias, President

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Company. It is well known, and acknowledged by the FDA, that The Upjohn Company has one of the most thorough systems in the industry for reporting medical events associated with their products. "20/20's" editorial treatment of this makes the company's diligence seem proof of a problem with Halcion, which it is not.

Mention was made in the program that "Dutch authorities pulled (Halcion) off the market after a rash of complaints about the drug's side effects." Although Upjohn provided "20/20" with an accurate and complete account of the events in Holland, you decided to focus on only the most sensational aspect of the situation and tell half the story.

For the record, in August 1979 the Dutch Registration College imposed a temporary six-month withdrawal of the product license for Halcion 0.25 mg and 0.5 mg tablets in Holland. The college's action followed intense public pressure, after allegations of unusual side effects associated with the use of the product were reported by a single Dutch psychiatrist.

In February 1980 the college announced that the license for 0.25 mg Halcion tablets could be reinstated if Upjohn would agree to include in its labeling a list of possible and unusual side effects. Upjohn refused to accept these conditions because they were unsubstantiated in world medical literature, in extensive clinical tests and in our worldwide experience with the product. (Pakes, G.E. "Triazolam: A Review of its Pharmacological Properties and Therapeutic Efficacy in Patients with Insomnia." *Drugs* 22: 104-105, 1981.)

Subsequently the Registration College cancelled the product license for 0.25 mg and 0.5 mg Halcion tablets. Upjohn filed an appeal with the Dutch Council of State in 1980, arguing that the college's decision was not based on scientific evidence.

On the recommendation of the Dutch Council of State, the Crown decided in June 1985 to cancel the decision made by the Registration College in February 1980. In arriving at this conclusion, the Crown held that the Dutch Registration College acted without adequate review of available data, and did not observe sufficient diligence when it cancelled the registration of Halcion. The council also considered, however, that the 1977 package insert for Halcion in Holland could not be reinstated without amendment in light of subsequent worldwide experience with benzodiazepines and product registrations since 1980. The Council suggested that Upjohn apply for a new product license for Halcion in Holland through the Registration College. Obviously the issue did not end with the Dutch government pulling the product off the market, as was stated in your broadcast.

John Sias, President

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Another sensationalized statement involved Halcion being among the top twenty drugs cited in emergency room cases. To put this information in the proper context, it would be appropriate to mention that aspirin, acetaminophen and alcohol in combination with other drugs rank higher than Halcion in the listing. Most importantly, the Drug Abuse Warning Network (DAWN), which publishes the data, makes no attempt to qualify the raw data. In other words, no cause-and-effect relationship is established between the drug and the reason for the emergency room visit. As an example, if a person attempted suicide by ingesting drain cleaner and was brought in to a hospital, traces of any medication in that person would be recorded in the DAWN data.

You also indicated that the FDA acknowledged receiving more complaints about Halcion than other sleeping pills. Was this put in the context that Halcion is by far the most prescribed hypnotic and that one would expect to receive more reports on a drug that is used significantly more than the others? It was not.

The safe and effective use of any medication involves at least three clear responsibilities. A pharmaceutical company must research, test, report on and manufacture safe medicines. Physicians are responsible for properly diagnosing health problems and, if deemed effective therapy, prescribing medications and discussing them with the patient. Patients are responsible for properly using medications according to physician directions.

When properly produced, prescribed and used, Halcion Tablets provide safe and effective treatment for short-term insomnia. This has been well documented in numerous clinical studies and well established in more than 10 years of general medical use.

Halcion represents a significant advance in safety over earlier agents, which were toxic, interfered with the effects of other medicines and carried a high potential for facilitating suicide. In 1984, the United States National Institute of Mental Health issued a "Consensus Summary on Drugs and Insomnia." It presents the conclusions of a panel of U.S. medical and scientific experts (and European observers) brought together to summarize advanced thinking about the proper treatment of insomnia.

In cases where medication is appropriate for sleep management, the report notes, benzodiazepines are preferable, and for short-term use the smallest effective dose of a rapidly eliminated hypnotic, like Halcion, should be used. The American Medical Association cites benzodiazepines as "the drugs of choice when an antianxiety, sedative, or hypnotic action is needed."

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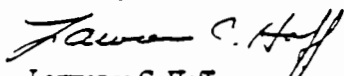
February 24, 1989

Sleep disturbances are very real medical problems. One-third of the U.S. population suffers from some degree of insomnia and 17 percent of them consider it severe. The consequences of insomnia include impaired daytime functioning, anxiety and emotional and behavioral disturbances among others. Lack of sleep and sleep-related factors appear involved in such catastrophic disasters as the Chernobyl nuclear disaster, Three Mile Island and the Space Shuttle Challenger accident. (Mitler, M. et al. "Catastrophes, Sleep and Public Policy: Consensus Report." *Sleep* 11:1, 1988, pp. 100-108.)

Halcion is an important therapeutic agent for the treatment of short-term and transient insomnia. When prescribed and used appropriately, it is effective and has a high margin of safety. Focusing on the anecdotal accounts of unusual and severe side effects does a great disservice to the millions of patients who are or have been treated successfully with this medication.

Upjohn has acted responsibly in researching, developing, marketing and reporting on Halcion. We are held accountable for what we do by the FDA, by doctors and by patients. We take these responsibilities very seriously.

Sincerely,



Lawrence C. Hoff  
The Upjohn Company

## APPENDIX C

**Beecham**  
laboratories

EXECUTIVE OFFICES 501 FIFTH STREET, BRISTOL, TENNESSEE 37620 615-754-5141

February 6, 1990

Dear Pharmacist:

From all accounts, this year's respiratory infection season may be one of the most active on record. Therefore, the number of prescriptions written for AMOXIL will be higher than ever. To make sure your inventories of AMOXIL are adequate for this increased demand, Beecham Laboratories would like to remind you of the exclusive reorder privileges you have qualified for.

By purchasing last year's Oral Antibiotic Offer, you are eligible for both free goods and extended dating on all reorders for AMOXIL.

**Free Goods**

To qualify for AMOXIL free goods, you need to order seven bottles, or any combination of seven bottles, of the same package size (100s or 500s) in AMOXIL Capsules to receive one bottle of AMOXIL Capsules in the lesser strength free. You need to order 24 bottles of AMOXIL Oral Suspension in the same package size to receive one bottle of AMOXIL Oral Suspension free.

Examples: If you order seven bottles of AMOXIL 250 mg or 500 mg Capsules, you will be invoiced for six bottles and receive one free bottle of AMOXIL Capsules in that same strength and package size.

If you order four bottles of 250 mg x 500 AMOXIL Capsules and three bottles of 500 mg x 500 AMOXIL Capsules or any combination totaling seven, you will be invoiced for a total of six bottles and receive one free bottle of 250 mg x 500 AMOXIL Capsules.

**Extended Dating**

All reorders will receive a 2 percent discount, 90 days, net 91 days dating.


To reorder, please contact your Beecham Sales Representative or phone 1-800-251-7040 (1-800-821-0279 Tennessee only).

**This exclusive reorder program ends March 31, 1990.**

Beecham will continue to maintain your trust by offering you quality products at competitive prices and providing you with outstanding service.

Thank you for your support and confidence in Beecham.

Sincerely,

  
Edwin M. Christensen  
Vice President, Sales

## APPENDIX D

**§ 4.2.8 *Pharmaceutical Manufacturers Association Code of Fair Practices in the Promotion of Drug Products\****

Recognizing the importance to the public health of providing the medical profession with accurate information on drug products, and the need to assure that PMA members, their employees and agents present such information fairly and objectively.

The Pharmaceutical Manufacturers Association hereby promulgates and adopts the following Code of Fair Practices in the Promotion of Drug Products as a revision of its 1958 Statement of Principles on the same subject:

**A. Code Standards****1. As used in this Code:**

- (a) The term "drug product" means any pharmaceutical or biological product intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in humans, or to affect the structure or any function of the human body, which is promoted and advertised to the medical profession rather than directly to the lay public.
- (b) The term "promotional communications" means (1) journal advertising, mailing pieces, and similar written materials (including, to the extent reasonably practicable, films, exhibits and similar visual presentations) directed to members of the medical profession by the pharmaceutical industry for the purpose of promoting a drug product and (2) written instructions and materials prepared for sales or professional representatives containing representations to be made by them to members of the medical profession. Where compliance with the requirements of this Code is not reasonably practicable within the format of a film, exhibit or similar visual presentation, written materials meeting those requirements shall be distributed to all members of the medical profession attending the presentation.
- (c) The term "medical profession" includes allied professions in the health field.

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\*These standards are dated September 1967 and are believed by the editor to be current.



2. Complete and accurate information concerning marketed drug products should be made available promptly to the medical profession. Promotional communications to the medical profession which include a description of indicated uses or dosage recommendations for a prescription drug product should also include a summary (or full disclosure where required by law) of side effects, precautions, warnings and contraindications, and of effectiveness for the described indicated uses. Such summary should have sufficient prominence in terms of type size, location and similar factors to provide reasonable assurance that it will be observed.
3. Statements in promotional communications should be based upon substantial scientific evidence or other responsible medical opinion. Claims should not be stronger than such evidence warrants. Every effort should be made to avoid ambiguity. Whenever statistical or background information or references to unpublished literature or observations are used in promotional communications, the source material should be available to the medical profession upon request.
4. Statements with respect to or quotations from medical literature or from the personal communications of clinical investigators in promotional communications should not distort the intended meaning of the author or the significance of the study.
5. Any comparison with other drug products should be made upon a valid scientific basis.
6. No public communication by a manufacturer shall be made with the intent of promoting a drug product as safe and effective for any use before the required approval of the drug product for marketing for such use is obtained. However, this provision is not intended to abridge the right of the scientific community and the public to be fully informed concerning scientific and medical progress. Thus it is not intended to restrict a full and proper exchange of scientific information concerning a drug product, including appropriate dissemination of investigational findings in scientific or lay communications media, nor to restrict public disclosure to stockholders and others concerning any

drug product as may be required or desirable under law, rule or regulation.

7. Promotional communications should have medical clearance before their release.

**B. Code Administration**

It is the unqualified intent of the Association that each member shall follow strictly the principles set forth in the Code. To that end the members of the PMA are encouraged to submit information to the President with respect to any alleged breach of this Code by any other member. On the basis of such information and any other information available to him, the President shall take appropriate action including, if required, referral of the information to an ad hoc committee of the Board. The committee shall be chosen by the Chairman of the Board unless the member company represented by the Chairman has submitted such information or is the subject of such information, in which case the President shall make the appointments. The General Counsel of the Association shall act as secretary of each ad hoc committee and shall report the committee's findings to the President who in turn<sup>89</sup> will refer the findings to the Board of Directors.

Any member firm which clearly and persistently violates the Code may be asked by the Board of Directors to resign from the Association.