

University of Pennsylvania Carey Law School

Penn Law: Legal Scholarship Repository

Faculty Scholarship at Penn Law


1995

FDA Reform and the European Medicines Evaluation Agency

Theodore Ruger

University of Pennsylvania Carey Law School

Follow this and additional works at: https://scholarship.law.upenn.edu/faculty_scholarship

 Part of the [Administrative Law Commons](#), [Comparative and Foreign Law Commons](#), [Food and Drug Law Commons](#), [Health Law and Policy Commons](#), [Pharmacy Administration, Policy and Regulation Commons](#), and the [Policy Design, Analysis, and Evaluation Commons](#)

Repository Citation

Ruger, Theodore, "FDA Reform and the European Medicines Evaluation Agency" (1995). *Faculty Scholarship at Penn Law*. 1295.

https://scholarship.law.upenn.edu/faculty_scholarship/1295

This Article is brought to you for free and open access by Penn Law: Legal Scholarship Repository. It has been accepted for inclusion in Faculty Scholarship at Penn Law by an authorized administrator of Penn Law: Legal Scholarship Repository. For more information, please contact PennlawIR@law.upenn.edu.

FDA REFORM AND THE EUROPEAN MEDICINES EVALUATION AGENCY

I. INTRODUCTION

The political change that swept through Washington in November 1994 has intensified an already contentious debate about the appropriate role of the federal government in regulating health and safety risks. The new Republican Congress has sought to challenge traditional patterns of administrative activity.¹ Not surprisingly, the Food and Drug Administration (FDA), with its sweeping regulatory authority over products accounting for 25 cents of every consumer dollar — over \$1 trillion annually² — has been one prominent target of conservative critics bent on deregulating America. House Speaker Newt Gingrich has called FDA Commissioner David Kessler a “thug and a bully” and supports efforts to relegate the FDA to the role of an oversight agency, with more intensive testing and certification done by private groups.³ Conservative organizations have aggressively accused the FDA of contributing directly to the deaths of patients who are left without lifesaving new drugs.⁴ In response to this furor, the Clinton administration has proposed its own, less drastic suggestions for reform.⁵

Although related to the general political climate in Washington, reform of the FDA’s drug approval process differs from typical “conservative” deregulation in important ways, because both the health risks and therapeutic benefits of prescription drugs are internalized by individual patients. Many federal agencies charged with regulating risk, like the Environmental Protection Agency, must weigh potential economic benefits accruing to particular sectors of society against generalized risk to healthy populations. The conflict is often framed as one between “the public” and the regulated industries. Prescription drugs, on the other hand, involve discrete amounts of risk and benefit

¹ Most notably in the short term, the Republicans have drafted a “rulemaking moratorium” bill, which would void hundreds of agency regulations promulgated since November 30, 1994. See Guy Gugliotta, *Ambiguity Rules the Day: GOP Move to Limit Regulations Yields Maze of Interpretations*, WASH. POST, Feb. 23, 1995, at A25.

² See Henry I. Miller, *The FDA and Regulatory Reform*, S.F. CHRON., Mar. 10, 1995, at A23.

³ Laurie McGinley, *GOP Takes Aim at FDA, Seeking to Ease Way for Approval of New Drugs, Medical Products*, WALL ST. J., Dec. 12, 1994, at A16.

⁴ As one critic asks somewhat hyperbolically, “If a drug that has just been approved by FDA will start saving lives tomorrow, then how many people died yesterday waiting for the agency to act?” Sam Kazman, *Deadly Overcaution: FDA’s Drug Approval Process*, 1 J. REG. & SOC. COSTS 35, 35 (1990).

⁵ The proposed changes include an allowance made for manufacturers to change the way they produce approved drugs without receiving FDA preclearance, elimination of required environmental assessments, removal of special requirements for insulin and antibiotic drugs, and other reforms. See BILL CLINTON & AL GORE, *REINVENTING MEDICAL DEVICE REGULATIONS passim* (1995).

that are assumed by individual patients.⁶ A tradeoff exists between the potential therapeutic gains from a new drug and the likelihood of an adverse reaction to that drug. The uncertain and contingent nature of illness and disease means that members of the public at large, as well as the FDA itself, have a difficult time striking this balance.

Moreover, the very meaning of "risk" with respect to diseased patients differs from similar assessments of safety risk to healthy populations, with consequent difficulties for any agency charged with defining an appropriate level of safety.⁷ How does one determine acceptable amounts of "risk" for a terminally ill AIDS or cancer patient? Even individuals in identical states of disease or illness may make widely differing decisions in the face of similar treatment risks.⁸

These unique features of drug regulation have produced unusual political coalitions to push for reform of the FDA's drug approval process. Joining conservative critics of regulation are patients' groups (particularly for people with certain prominent diseases like cancer and AIDS), which have frequently decried the FDA's reluctance to grant swift approval to promising new drugs.⁹ Similarly, physicians and, increasingly, managed-care insurers are often in tension with the FDA over who is best placed to make particularized judgments about a drug's safety and effectiveness. Although the FDA rigorously scrutinizes all *new* drugs before approval, the agency allows doctors wide latitude to prescribe drugs approved for one particular use in unapproved ("unlabeled") ways to treat other conditions.¹⁰

Because prescription drug injuries are often so conspicuous, whereas the adverse health effects of nonapproval are frequently invisible, the FDA's incentive structure naturally tends toward caution. An FDA employee working on a New Drug Application (NDA) has every reason to fear the death or severe injury that could follow from an ill-advised drug approval. Conversely, the lack of concrete, identifiable

⁶ One exception to this paradigm is the field of vaccines for contagious diseases, which have public health dimensions beyond the individual patient.

⁷ In a rare judicial discussion of this quandary, the Tenth Circuit held that the Food, Drug & Cosmetic Act's standards for new drug approval had no application to terminally ill cancer patients. *See Rutherford v. United States*, 582 F.2d 1234, 1237 (10th Cir. 1978). The Supreme Court unanimously reversed, holding that "no exception for terminal patients may be judicially implied." *United States v. Rutherford*, 442 U.S. 544, 559 (1979).

⁸ In addition to different levels of risk aversion with respect to new drugs, patients might have widely different attitudes about the pain and suffering caused by existing therapies.

⁹ *See, e.g.*, Gina Kolata, *An Angry Response to Actions on AIDS Spurs F.D.A. Shift*, N.Y. TIMES, June 26, 1988, at 1, 22.

¹⁰ This policy is codified at 21 C.F.R. § 312.2(d) (1994). Some estimates find that up to 50% of all current prescription drug therapies involve unapproved use of approved drugs. *See* Stephen Chapman, *The FDA and Other Enemies of Public Health*, CHI. TRIB., Feb. 26, 1995, § 4, at 3. Chapman and other critics of the FDA assert that if the dire health consequences that defenders of the current system predict upon deregulation were legitimate, they would be already apparent as a result of unregulated prescription drug use. *See id.*

injury often makes the likely ramifications of an erroneous non-approval scant, if not non-existent.

This cautious attitude is replicated in the agency's relationship with Congress. Members of Congress, concerned with public opinion, often hesitate to advocate approvals of specific new drugs which might subsequently produce well-documented adverse effects on consumers.¹¹ On the other hand, the detrimental health effects of non-approval often are difficult to quantify and fail to galvanize public opinion. Proponents of strict drug regulation quite adeptly use the tragic and publicized nature of many drug injuries to sway Congress toward tight oversight of FDA drug approvals.¹²

This Note will briefly examine the FDA's current approval process for new drugs, some of its problems, and some recent suggestions for reform. The Note will argue that complete deregulation of pharmaceuticals is too severe, at least with respect to judgments of new drug safety. Instead, Congress and the FDA should take advantage of a new opportunity for international cooperation presented by the European Community's recent establishment of a centralized drug regulatory body, the European Medicines Evaluation Agency (EMA). By exploring opportunities for regulatory harmonization and mutual recognition of new drugs with this new superagency, the FDA could potentially speed access to new drugs while continuing to ensure public safety.

Part II below sets forth the broad outlines of the FDA's regulatory scheme for new drugs and lists some problems with the current regime. Part III examines some FDA reform proposals currently on the public agenda. Part IV then explores the option of a mutual recognition scheme with the new EMA, and Part V assesses some potential difficulties with that approach. A brief conclusion follows.

II. FDA REGULATION AND ITS PROBLEMS

The development of a new drug, from laboratory inception to final FDA approval, is a long and costly process. After completing years of carefully controlled and regulated clinical trials, drug manufacturers submit a New Drug Application (NDA) to the FDA for review.¹³

¹¹ For example, Rep. Joe Barton (R-Texas), chair of a House Commerce subcommittee that oversees the FDA, has expressed this sentiment: "The FDA may be unique [because its decisions may have] life or death consequences. . . . If they were to approve a defective drug, it could kill people. Other regulatory agencies don't have as immediate a negative impact." Doug Levy, *Producing the FDA: Both Sides Say Lives Are at Stake*, USA TODAY, Mar. 7, 1995, at 1D.

¹² See C. Frederick Beckner, III, Note, *The FDA's War on Drugs*, 82 GEO. L.J. 529, 548-49 (1993). Drug manufacturers, who would ordinarily exert strong interest group pressure on the FDA, face a collective action problem because each company already in the market benefits from the high barriers to new entry imposed by the FDA's regulatory process. See *id.* at 549.

¹³ Subject to a few exceptions, pharmaceuticals that are lawfully sold in the United States today fall into one of two categories: drugs that were generally recognized as safe and effective

Since 1962, the FDA has administered a pre-marketing approval system, whereby new therapeutic compounds must satisfy certain statutory criteria for safety and effectiveness and must receive explicit agency approval before going on the market.

The pre-1962 system differed from the current one in two important ways. First, new drugs did not require explicit FDA approval to go on the market; mere agency silence for a certain amount of time after the NDA filing was sufficient.¹⁴ Second, prior to 1962 the FDA assessed only the safety of new drugs, not their effectiveness.¹⁵

Like other episodes of drug legislation, the Drug Amendments of 1962 were enacted in the wake of a public health tragedy. In 1960 Dr. Frances Kelsey, an FDA examiner, delayed the approval of an NDA for the drug thalidomide due to a lack of sufficient safety information.¹⁶ In 1961 doctors in Europe discovered that thalidomide, which was marketed there, was responsible for a significant number of birth defects.¹⁷ The news helped to generate public support for the drug reform legislation that was already pending in the U.S. Senate.¹⁸

Under the current regime, a new drug must satisfy statutory standards of both safety and effectiveness to receive FDA approval. Section 505(d) of the Food, Drug & Cosmetic Act (FDCA) requires that to be approved, a drug must be shown "by all methods reasonably applicable" to be "safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling."¹⁹ The same statutory section also requires "substantial evidence" that the drug is effective in its intended use.²⁰ Based on these standards and the evidence contained in each NDA, the FDA makes a decision on each drug application. The agency is not required to explain its reasons for approval or denial, and it may require certain post-approval research on the drug's effects.²¹

prior to the Drug Amendments of 1962 and drugs that have satisfied the FDA's NDA procedures. See JAMES R. NIELSEN, *HANDBOOK OF FEDERAL DRUG LAW* 27 (2d ed. 1992); see generally PETER B. HUTT & RICHARD A. MERRILL, *FOOD AND DRUG LAW* 513-37 (2d ed. 1991) (describing the NDA application and approval process for new drugs).

¹⁴ See Peter B. Hutt, *The Regulation of Pharmaceutical Products in the USA*, in *PHARMACEUTICAL MEDICINE* 211, 216-17 (Denis M. Burley, Joan M. Clarke & Louis Lasagna eds., 2d ed. 1994).

¹⁵ See *id.* at 217.

¹⁶ See PETER TEMIN, *TAKING YOUR MEDICINE: DRUG REGULATION IN THE UNITED STATES* 123 (1980).

¹⁷ See *id.*

¹⁸ See *id.* at 124.

¹⁹ 21 U.S.C. § 355(d) (1988).

²⁰ See *id.* The statute defines "substantial evidence" of effectiveness as "evidence consisting of adequate and well-controlled investigations . . . that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof." *Id.*

²¹ See HUTT & MERRILL, *supra* note 13, at 531, 537.

The FDA's method of enforcing these standards of safety and effectiveness has garnered significant criticism of late. Gaining approval of an NDA can cost hundreds of millions of dollars and can take several years. One estimate placed the 1987 average research, development, and administrative costs of taking a new chemical compound through the full NDA process at \$231 million.²² In the last year before NDA approval, the average "carrying cost" (of capital) amounts to approximately \$31 million.²³

Much debate has centered on other, more indirect costs of drug regulation. Drug companies embark on the development of new compounds in response to perceived demand from the medical community of doctors and patients.²⁴ During the decade-long research and approval process, numerous patients would presumably seek the therapeutic gains from a new compound were it available on the market. The unavailability of a new drug caused by the FDA's approval strictures may cause significant detriment to these patients.

The exact magnitude of this therapeutic loss is uncertain. A landmark study in this regard, performed over 20 years ago by economist Sam Peltzman, identified a decline in new drug innovation in the United States and attributed that decline to the drug amendments of 1962.²⁵ For example, his research indicated that an average of 42 new chemical entities were marketed each year in the fifteen years prior to 1962, compared with only sixteen in the decade following amendment.²⁶ Based on price information about drugs that were currently on the market, Peltzman estimated the therapeutic loss due to FDA regulation at over \$450 million per year.²⁷

²² Joseph A. DiMasi, Ronald W. Hansen, Henry G. Grabowski & Louis Lasagna, *Cost of Innovation in the Pharmaceutical Industry*, 10 J. HEALTH ECON. 107, 125-26 (1991).

²³ Hutt, *supra* note 14, at 240. Research suggests that the high capital expenditures required to comply with FDA regulatory requirements contribute to a decline in research and development investment below optimal levels. See, e.g., MEIR STATMAN, *COMPETITION IN THE PHARMACEUTICAL INDUSTRY: THE DECLINING PROFITABILITY OF DRUG INNOVATION* 61-62 (1983).

²⁴ To provide incentives for drug companies to develop and manufacture products for rare diseases that would otherwise produce insufficient patient demand to support drug development, Congress in 1983 enacted the Orphan Drug Act. See 21 U.S.C. § 360aa-ee (1988). These provisions allow tax credits for money spent on clinical testing of drugs for a "rare disease or condition," defined as one that affects fewer than 200,000 persons nationwide, or drugs that are expected to cost more than they will earn on the market. See 21 U.S.C. § 360bb(a)(2); 26 U.S.C. § 28 (1988). Also, the Act provides manufacturers with seven years of post-approval market exclusivity for any unpatentable orphan drug. See 21 U.S.C. § 360cc(a) (1988); HUTT & MERRILL, *supra* note 13, at 566.

²⁵ "[T]he amendments' proof of efficiency and clinical testing requirements impose costs on the drug development process which discourage new drug development." *Regulation of Pharmaceutical Innovation, 1973: Hearings Before the Subcomm. on Monopoly of the Senate Comm. on Small Business*, 93d Cong., 1st Sess. 9802, 9803-07 (1973) (statement of Sam Peltzman).

²⁶ See *id.*

²⁷ See *id.*

Other, more recent studies suggest that regulatory delays may have a negative impact on patient life expectancy and quality of life. One advocate of deregulation asserts that while the FDA was considering the NDA for misoprostol, a drug used to treat gastric ulcers, 8,000 to 15,000 patients died from that condition.²⁸ Pharmacologists William Wardell and Louis Lasagna found that the drug nitrazepam, which was approved in the United States five years after it had been approved in Britain, might have saved thousands of American lives in that five-year span.²⁹ The authors noted that “[i]ntroduction of a new drug that produced fatalities anywhere approaching this magnitude would be regarded as a major disaster, but the undoubted occurrence of deaths through failure to introduce a drug has so far gone unremarked.”³⁰

Numerous cross-national analyses have indicated that the FDA’s regulatory scheme is more cumbersome than that of other countries. The aforementioned 1975 study by Wardell and Lasagna popularized the notion of the “drug lag” between Britain and the United States, meaning that identical new compounds took significantly longer to wend their way through the rigorous American process.³¹ The authors concluded that although the higher strictures of the FDA process may have resulted in incremental safety gains, these benefits were outweighed by the loss of therapeutic potential from not-yet-approved drugs.³² More recent data indicates that Britain and other industrialized nations may still have a significant lead on the United States in the assessment and approval of beneficial drugs. In 1984 the median time in Britain for granting of a “new product license” was twelve months,³³ the median time for the FDA’s NDA process was 31.1 months.³⁴

Some skepticism is appropriate in considering the above statistical evidence. For instance, a significant portion of the cost and time involved in developing a new chemical compound and bringing it to market would be incurred by pharmaceutical manufacturers even in

²⁸ See Kazman, *supra* note 4, at 47–48.

²⁹ See WILLIAM M. WARDELL & LOUIS LASAGNA, REGULATION AND DRUG DEVELOPMENT 72–73 (1975).

³⁰ *Id.* at 73.

³¹ See *id.* at 77.

³² See *id.* at 105. According to Wardell and Lasagna: In view of the clear benefits demonstrable from some of the drugs introduced into Britain, it appears that the United States has lost more than it has gained from adopting a more conservative approach than did Britain in the post-thalidomide era. *Id.*

³³ See J.P. Griffin, *Objectives and Achievements of Regulations in the U.K.*, in INTERNATIONAL MEDICINES REGULATION: A FORWARD LOOK TO 1992, at 73, 87 tbl. 8.8 (Stuart R. Walker & John P. Griffin eds., 1989) [hereinafter INTERNATIONAL MEDICINES].

³⁴ See J.R. Crout, *Objectives and Achievements of Regulations in the USA*, in INTERNATIONAL MEDICINES, *supra* note 33, at 117, 130.

the absence of any regulation at all.³⁵ Also, defenders of the current system assert that small but significant safety gains *are* realized from the FDA's current cautious approach.³⁶ However, on balance research does suggest that regulatory systems in other industrialized nations achieve a generally safe drug supply while avoiding some of the delay of the FDA process.

The FDA has responded to the problems in its new drug approval system with varying degrees of success. Pressure from organized patient groups has led the agency to loosen restrictions and allow some patients to be treated with new drugs that are still in the investigational stage.³⁷ Also, the FDA has sought to accelerate the approval process for promising new drugs for certain life-threatening diseases.³⁸ The FDA claims that such efforts have reduced approval times and shortened the drug lag. According to the agency, its median approval time for new drug applications fell from 26.7 months in 1993 to 19 months in 1994.³⁹ Furthermore, for new pharmaceuticals processed under the Prescription Drug User Fee Act of 1992,⁴⁰ the median time was 13.5 months — and only 10.4 months for “therapeutically important indications.”⁴¹

Some experts question the FDA's statistics and claim that the time for NDA approval is decreasing only because the FDA is asking for substantially more clinical data before it starts its NDA review “clock.”⁴² The Center for the Study of Drug Development at Tufts University found that from 1990 to 1992, although median review time for “important” new drugs was 20 months instead of 31 for other products, development times for the former group were three years longer.⁴³ According to Dr. Louis Lasagna, head of the Center, the length between drug discovery and NDA approval “is not shortening.”⁴⁴

³⁵ For a description of the clinical testing process for new drugs, see HUTT & MERRILL, *supra* note 13, at 513–19.

³⁶ See *infra* p. 2023.

³⁷ See Hutt, *supra* note 14, at 230. The FDA allows such early treatment when, in addition to other factors, the drug is intended to treat a serious or immediately life-threatening disease and when there is no satisfactory alternative. See *id.* To supplement such “compassionate use” INDs, the FDA also permits “parallel track” procedures for AIDS when no therapeutic alternative exists and individuals cannot participate in individual clinical trials. *Id.*

³⁸ See *Hearings Before the Senate Committee on Labor and Human Resources*, 104th Cong., 1st Sess. (1995) (statement of David Kessler, FDA Commissioner) [hereinafter *Kessler Testimony*].

³⁹ See *id.*

⁴⁰ Pub. L. No. 102-571, 106 Stat. 4491 (codified in scattered sections of 21 U.S.C. (Supp. IV 1992)).

⁴¹ See *Kessler Testimony*, *supra* note 38.

⁴² See John Carey, *Is the FDA Hooked on Caution?*, BUS. WEEK, Jan 30, 1995, at 72, 73.

⁴³ See *id.*

⁴⁴ Chapman, *supra* note 10, at 3.

The FDA deserves credit for its attempts to respond to the concerns of specific groups and to improve on aspects of the new drug approval process generally. Yet piecemeal reform efforts that maintain the current FDA structure carry certain limitations, many resulting from the particular regulatory history and environment of the agency. As described above, the incentives for caution that FDA investigators face may mean that internal reforms will meet with diminishing marginal returns.

III. DEREGULATORY REFORMS AND THEIR LIMITATIONS

The problems associated with the drug regulatory process have spurred a number of conservative thinkers to advocate a radical restructuring of the FDA's role. Not surprisingly, advocates for massive deregulation are emboldened by the current political climate in the nation's capital. The unifying theme of many conservative proposals, whether they originate within or outside of Congress, is an almost complete elimination of the FDA's power to prevent a new drug from reaching the market. Advocates of deregulation propose reconfiguring the FDA as a mere certification agency, with the authority to grant or withhold its "stamp of approval" for a particular drug or medical device but not to proscribe sales altogether.⁴⁵ This agency construct would parallel the role of the Underwriters Laboratories and other private groups, which assess and certify quality and safety standards for a wide range of electronic and mechanical consumer products. According to proponents, such a regulatory scheme would allow patients and their physicians to make informed decisions regarding drug consumption — by using a drug that did not have FDA certification, a patient would accept the risks of safety problems or ineffectiveness. In some ways, such a dual system already exists, as the FDA does not prohibit individual patients from receiving unapproved drugs from abroad.⁴⁶

Related reform proposals urge a greater role for the medical profession in assessing the safety and efficacy of new drugs. For the majority of this century, decisions about drug efficacy were left completely in the hands of prescribing physicians. Some commentators now feel that the changing structure of the health care industry makes a return to greater provider autonomy appropriate. William Wardell, long an authority in the field of drug regulation, has suggested that the growth of managed care medicine, in which health care providers bear the

⁴⁵ See Reginald Rhein, *Congress, Health Care Groups Push for Faster FDA*, *Biotechnology Newswatch*, Feb. 6, 1995, available in LEXIS, News Library, Curnws File.

⁴⁶ Since 1977, the FDA has not detained unapproved new drugs imported for personal use. See Hutt, *supra* note 14, at 238. Given the high costs of many such imported drugs and the fact that they are often not covered by U.S. health insurance plans, access to unapproved imported drugs is often out of reach for less wealthy Americans.

financial risk of ineffective treatment, might result in a shift of the actual decisionmaking power about new drugs from the FDA to managed care institutions.⁴⁷

The above proposals for reform, and like measures, share a common distrust of the FDA's ability to balance the risks and benefits of new drugs appropriately. Such proposals thus seek to shift the responsibility of striking the balance to other groups — consumers, private boards, and health care providers — which purportedly can do it better. None of these groups, however, possess sufficient incentives or information to supplant the FDA as a guarantor of a new drug's safety and efficacy. Managed care health organizations are concerned first and foremost with the cost-effectiveness of any new drug therapy, rather than with the safety and efficacy of a new drug, and therefore may not always act as "honest agents" for patients. Patients themselves, as consumers of new drugs, may lack sufficient information to assess adequately when to avoid a new drug that has not been "certified" by the FDA. Clinical assessments of drug performance are often complex and difficult to interpret, which could present problems of understanding for patients, even with the assistance of individual physicians. Finally (and ironically) the apparent success in this Congress of tort reform that would impose caps on nonpecuniary and punitive damages, undercuts a basic argument of critics of the FDA, many of whom also supported tort reform. Whereas before it could be argued that the tort system existed as a formidable independent check against unsafe drugs, the new caps on nonpecuniary damages, coupled with preexisting obstacles to proof of causation and damages in drug injury actions, cast doubt on whether tort law can effectively deter drug manufacturers from discounting safety.⁴⁸ Some form of government regulatory oversight is needed to protect the public from unsafe drugs.

The proposal that follows accepts the view that the current FDA structure may lead to the overregulation of beneficial new drugs. However, rather than advocating the complete removal of pharmaceuticals from the purview of government regulation, this proposal explores ways in which collaboration and even "competition" with a counterpart government agency in Europe might render the FDA more responsive to popular demand for beneficial therapies while maintaining its role as a guarantor of safety.

⁴⁷ See William Wardell, Transcript of the Conference on Reforming the Food and Drug Administration: The Pharmaceutical Approval Process 21-22 (Mar. 10, 1995) (transcript available in Harvard Law School Library); see also William R. Sage, Note, *Drug Product Liability and Health Care Delivery Systems*, 40 STAN. L. REV. 989, 992-98, 1005-08, 1011-14 (1988) (describing the growth of capitated managed care systems and discussing the implications for drug product liability).

⁴⁸ SWAT

IV. THE EMEA AND PROPOSALS FOR REFORM

The United States is not alone in grappling with the tradeoff between the risks and benefits of faster approval of new drugs. The European Community recently established a centralized agency in an effort to standardize and accelerate the approval process for certain new drugs.⁴⁹ The European Medicines Evaluation Agency (EMA) will act both as a centralized approval agency, with its decisions binding on all member states, and as an oversight body for a more decentralized mutual recognition procedure, whereby approval of a new drug by the authority of one member state will, absent cause, be sufficient for approval in all other member states.⁵⁰

Under the new EC and EMA system, three types of new drug application procedures operate simultaneously. First, an applicant may submit information concerning a new drug for consideration by the EMA itself.⁵¹ The EMA is then supposed to return a ruling — binding on the entire European Community — within 300 days. A second, more decentralized route allows companies to apply to one specific national drug regulatory agency and send a copy of the application to other member states.⁵² If the drug application is approved by the first nation, other nations are required either to recognize the new drug for sale within their borders or to file a formal objection for adjudication by the EC. Finally, companies wishing to market a drug in only one member state are free to use traditional national application procedures.⁵³

This Section proposes two reforms of the FDA's new drug approval process in light of the creation of the EMA. First is the modest suggestion that approval of a new drug by the EMA should constitute "substantial evidence" of a drug's efficacy sufficient to satisfy Section 355(d) of the FDCA. Second is a more fundamental reform that would require the FDA to grant approval, within a specified statutory time period, of any new drug certified by the EMA unless the FDA could show that the drug might be *unsafe* or *ineffective*. Both of these suggested reforms would require a degree of internationalization which to date has been notably absent at the FDA. But both changes offer hope for quicker access to beneficial drugs while avoiding the grave safety risks posed by unrestrained deregulation.

⁴⁹ See Richard F. Kingham, Peter W.L. Bogaert & Pamela S. Eddy, *The New European Medicines Agency*, 49 FOOD & DRUG L.J. 301, 301 (1994).

⁵⁰ See *id.* at 304-12.

⁵¹ This centralized approval process is *required* for certain biotechnology products. See *Pharmaceuticals: European Agency to Start Processing Application Forms Next January*, Multinational Service, May 10, 1994, available in LEXIS, News Library, Curnws File [hereinafter Multinational Service].

⁵² See Multinational Service, *supra* note 51.

⁵³ See *id.* During a transition period lasting through 1998, a company may also use national procedures for simultaneous applications to several different states.

A. EMEA Approval as "Substantial Evidence" of Efficacy

The EMEA's approval of a new drug for sale throughout Europe should satisfy the FDCA's substantial evidence standard for effectiveness. Like the FDA, the EMEA requires proof of effectiveness and mandates high standards of research and scientific evidence that comport with the "adequate and well-controlled studies" language of Section 355(d) of the FDCA.

Legislative history indicates that Congress did not intend the FDCA's efficacy requirement to be an insurmountable barrier for promising new drugs. Prior to the passage of the 1962 Amendments, the Senate Judiciary Committee debated the proper standard for drug efficacy. Some members proposed a "preponderant evidence" threshold, while others advocated the lower "substantial evidence" standard.⁵⁴ Under the former standard, a drug would not be recognized as effective "unless it represented the *preponderant* view of experts qualified by training and experience in the subject that the claim was supported."⁵⁵ However, the committee (and eventually both Houses of Congress) opted for the less stringent substantial evidence test. Recognizing that "in the difficult area of drug testing and evaluation there will frequently, if not usually, be a difference of responsible opinion," the Senate Committee stated that "the existence of such a difference should not result in disapproval of a claim of effectiveness if it is supported by substantial evidence."⁵⁶

Whatever one's opinion regarding the weight the FDA should give to EMEA determinations on matters of safety, the European agency's efficacy determination should satisfy the FDCA's substantial evidence threshold. The similar requirements of clinical review and scientific rigor employed by the agencies suggest that an EMEA determination of a drug's effectiveness fits the FDCA's terms. Because the European standard includes a third requirement, "quality," it may even prove more rigorous than the American test.⁵⁷

Finally, recent developments in the American health care industry may support a reduction of the emphasis on intense FDA scrutiny of new drug effectiveness. For most of the FDA's history, the agency was charged only with screening out unsafe drugs; determinations of efficacy in prescription drugs were left to prescribing physicians.⁵⁸

⁵⁴ S. REP. NO. 1744, 87th Cong., 2d. Sess., pt. 2 (1962), reprinted in 21 U.S.C.A. § 321 (1981).

⁵⁵ *Id.* (emphasis added).

⁵⁶ *Id.*

⁵⁷ See Eric M. Katz, *Europe's Centralized New Drug Procedures: Is the United States Prepared to Keep Pace?*, 48 FOOD & DRUG L.J. 577, 585 (1993).

⁵⁸ See Hutt, *supra* note 14, at 217; TEMIN, *supra* note 16, at 127-28. To facilitate these determinations by physicians and patients, the FDA imposed on drug producers a panoply of labeling and disclosure requirements, many of which remain in force today. See Hutt, *supra* note 14, at 236.

However, Congress's 1962 amendments to the FDCA added an efficacy review for drugs already on the market and all new drug applications. At that time, physicians were no longer thought to be effective agents for patients, because the individual prescribing physician did not bear the costs of expensive prescription drugs and typically lacked the expertise required to pass judgment on a range of prescription drugs.⁵⁹

Today, in contrast, many physicians work for sophisticated managed care organizations which do bear the costs of drug treatment. In such arrangements, the managed care provider accepts the burden of all treatment costs for patients in return for a fixed, or "capitated," annual fee. As a result, physicians in managed care plans have strong incentives not to prescribe ineffective drugs.⁶⁰ Although the incentive structure of managed care entities is such that independent FDA review is still necessary for new drugs — particularly with respect to new drug *safety* — the fact that most Americans will be covered by capitated insurance plans should temper concern over widespread use of *ineffective* drugs. The FDA's reliance on EMEA approval of a new drug as "substantial evidence" of that drug's effectiveness would thus comport with the values underlying the statutory requirement of effectiveness.

B. *Mutual Recognition Between the FDA and the EMEA*

A more sweeping reform would involve the development of a qualified mutual recognition system between the FDA and the EMEA. This system might work as follows.⁶¹ Drug companies would be required to file application papers with both agencies. Upon approval of a new prescription drug by the EMEA,⁶² the FDA would have a certain period — perhaps 180 days — in which to object to the marketing of that compound in the United States. If the FDA did not respond within the statutory time period, the new drug would automatically gain approval for the U.S. market; if the FDA did object, the agency would bear the statutory burden of proving legitimate doubts about a new drug's safety or efficacy.

Such a cooperative international approach to drug regulation seems to be at odds with the FDA's mandate and practice for most of this

⁵⁹ See TEMIN, *supra* note 16, at 122–23.

⁶⁰ A fully capitated provider that prescribes ineffective drugs bears two distinct types of costs — the cost of the drug itself and the indirect treatment costs of patients who do not become well.

⁶¹ Some of these elements parallel the mutual recognition system in place among EC nations. However, unlike that system, in which decisions to prevent marketing of a drug that has been approved in other countries are subject to review by an EC-wide body, the FDA would have the right to refuse approval if it could prove doubts about safety.

⁶² The system I propose would be mutual, in that the EMEA would also have to rule quickly on an application after a drug was approved by the FDA. For the sake of clarity in this discussion, I will use the example of the FDA responding to an EMEA approval.

century. The FDA has traditionally been regarded as the world's most influential pharmaceutical regulatory body⁶³ and has thus been able essentially to dictate scientific standards and clinical requirements to drug manufacturers the world over. The profit potential from the American market has induced international manufacturers to comply with the FDA's high regulatory barriers.

With the advent of an operative EMEA, however, the FDA no longer oversees the world's largest integrated pharmaceutical market.⁶⁴ The nations of the European Community account for one third of the world market in pharmaceuticals; in 1988 this market was worth \$38 billion.⁶⁵ The existence of this huge integrated market threatens to undermine the FDA's position of regulatory leadership, and U.S. patients ultimately may suffer from an even greater "drug lag" if pharmaceutical manufacturers tailor their clinical research and new drug applications to satisfy EMEA standards.

The FDA itself has recently taken steps toward international harmonization of some of its requirements. A 1985 agency regulation allows the use of certain approved studies from abroad.⁶⁶ In recent years, the agency has approved at least five NDAs based on foreign data alone, and nine based upon a mixture of foreign and domestic clinical trials.⁶⁷

Moreover, the United States, Japan, and the EC have been working to harmonize their respective requirements for new drug research and applications. In November 1991, the three governments met at the first International Conference on the Harmonization of Technical Regulation.⁶⁸ This conference standardized technical issues of testing and evaluation and laid a framework for future collaboration.⁶⁹ More recently, the EMEA has stated that it will continue to explore the development of harmonization and mutual recognition programs with the United States and Japan.⁷⁰

V. ANALYSIS AND PROBLEMS

Any effort to develop a degree of harmonization and mutual recognition with a foreign regulatory body like the EMEA is sure to face

⁶³ See Katz, *supra* note 57, at 578-79.

⁶⁴ See *id.* at 579.

⁶⁵ See Louis H. Orzack, Kenneth I. Kaitin & Louis Lasagna, *Pharmaceutical Regulation in the European Community: Barriers to Single Market Integration*, 17 J. HEALTH POL., POL'Y & LAW 847, 848 (1992).

⁶⁶ See 21 C.F.R. §§ 312.120, 314.106 (1994).

⁶⁷ See Katz, *supra* note 57, at 581.

⁶⁸ See David W. Jordan, Note, *International Regulatory Harmonization: A New Era in Prescription Drug Approval*, 25 VAND. J. TRANSNAT'L LAW 471, 492-93 (1992); Katz, *supra* note 57, at 580.

⁶⁹ See Jordan, *supra* note 68, at 492-95.

⁷⁰ See *A Drug Tsar is Born*, THE ECONOMIST, May 7, 1994, at 74.

significant criticism. These critiques could take several forms — from structural constitutional difficulties with delegating decisionmaking authority to a foreign government to more subjective concerns about safety risks to the American public. Many of these concerns can be mitigated by a careful structuring of mutual recognition procedures.

A. *The Nondelegation Dilemma*

For most students of administrative law, the constitutional doctrine of nondelegation exists as a historical footnote rather than as a contemporary check on administrative authority. Stated in its purest form, the nondelegation doctrine limits the ability of Congress to delegate to statutorily created administrative agencies the legislative powers vested in it by Article I of the Constitution.⁷¹ However, on only two occasions in this century has the Supreme Court invalidated, on Article I grounds, an act of Congress which delegated legislative authority to the President or an administrative agency;⁷² both of those instances occurred in the early years of the New Deal.⁷³

The Court has set limits on the ability of Congress to delegate authority beyond the bounds of the federal government. For instance, in *Carter v. Carter Coal Co.*,⁷⁴ the Court invalidated a statute that allowed a majority of miners and mine owners to agree on maximum hours and minimum wage rates that would be binding on *all* producers.⁷⁵ Although the Supreme Court has not explicitly addressed the issue of delegation to foreign powers, similar constitutional concerns would apply to any agreement that enabled the EMEA to bind the FDA to a particular decision. For example, some scholars have argued that Article 43 of the United Nations Charter, which authorizes the United Nations Security Council to execute an agreement whereby U.S. forces would serve under foreign command, might violate the

⁷¹ "All legislative Powers herein granted shall be vested in a Congress of the United States . . ." U.S. CONST. art. I, § 1.

⁷² See *A.L.A. Schechter Poultry Corp. v. United States*, 295 U.S. 495, 541–42 (1935); *Panama Refining Co. v. Ryan*, 293 U.S. 388, 430 (1935).

⁷³ Although the Court has not explicitly invoked the nondelegation doctrine to overturn an act of Congress, the doctrine may have some continuing vitality as a limiting principle on administrative authority. In one 1980 concurrence, then-Justice Rehnquist stated that "[w]e ought not to shy away from our judicial duty to invalidate unconstitutional delegations of legislative authority solely out of concern that we should thereby reinvigorate discredited constitutional doctrines of the pre-New Deal era." *Industrial Union Dep't, AFL-CIO v. American Petroleum Inst.*, 448 U.S. 607, 686 (1980) (Rehnquist, J., concurring).

⁷⁴ 298 U.S. 238 (1936).

⁷⁵ The Court stated that "[t]his is legislative delegation in its most obnoxious form; for it is not even delegation to an official or an official body, presumptively disinterested, but to private persons whose interests may be and often are adverse to the interests of others in the same business." *Id.* at 311. In this respect a "delegation" to the EMEA, in the form of some limited mutual recognition procedure, would be distinguishable, because the EMEA's "interests" — a safe and beneficial supply of pharmaceuticals — are closely related to those of the FDA.

Commander in Chief Clause⁷⁶ of the Constitution or Congress's Article I power to declare war.⁷⁷

Case law suggests that a system of mutual recognition with the EMEA would be constitutional so long as the FDA retained the final authority to object to, or "veto," particular new drugs. For example, federal circuit courts have upheld the Maloney Act,⁷⁸ which authorizes private self-regulation of the securities industry, against challenges of unconstitutional delegation.⁷⁹ In so doing, the courts have emphasized that although the regulatory scheme permits substantial rulemaking and adjudicatory authority by private industry associations, the statute is constitutional because the Securities and Exchange Commission has final authority to approve or disapprove the actions of these private bodies on appeal.⁸⁰

Based on this analysis, at least two structures for greater mutual recognition between the FDA and the EMEA would likely pass constitutional scrutiny. First, the FDA could itself decide to give deference to EMEA findings on many new drugs as a policy matter. In negotiations with the EMEA, the FDA could agree to a course of cooperation without any legally binding agreement.⁸¹ Alternatively, Congress could statutorily define an appropriate evidentiary standard by which the FDA should assess EMEA determinations and could set an abbreviated statutory time frame for decisions on EMEA-approved drugs, so long as final power to reject a new drug remained with the FDA.

B. Safety Concerns

Critics of a liberalized mutual recognition program will likely assert numerous pragmatic difficulties with such a system. The foremost of these relates to the safety dangers posed by a reduction of the FDA's current regulatory authority over new drugs. As three leading

⁷⁶ U.S. CONST. art. II, § 2, cl. 1.

⁷⁷ See Michael J. Glennon & Allison R. Hayward, *Collective Security and the Constitution: Can the Commander in Chief Power Be Delegated to the United Nations?*, 82 GEO. L.J. 1573, 1587-99 (1994). Glennon and Hayward argue that the initial issuance of an Article 43 agreement by the U.N. Security Council does not raise delegation problems, because the President has the power to exercise the United States's veto power as a permanent member of the Council. See *id.* at 1594. However, an unconstitutional infringement on the Commander in Chief power might occur subsequently, if U.S. troops are put under the command of a foreign leader and the President's power to recall American troops is constrained by the U.N. agreement. See *id.*

⁷⁸ 15 U.S.C. § 780-3 (1988 & Supp. V 1993).

⁷⁹ See Ira P. Robbins, *The Legal Dimensions of Private Incarceration*, 38 AM. U. L. REV. 531, 551 (1989).

⁸⁰ See *id.* at 551-53 (citing *Todd & Co. v. SEC*, 557 F.2d 1008 (3d Cir. 1977) and *R.H. Johnson & Co. v. SEC*, 198 F.2d 690 (2d Cir. 1952)).

⁸¹ This course of action is similar to that employed by the United States in certain arms control contexts. See Glennon & Hayward, *supra* note 77, at 1600. For example, such parallel policy declarations were used by the United States and the Soviet Union to extend the arms control provisions in the strategic arms limitation talks (SALT).

members of Congress wrote in response to Bush Administration proposals for greater regulatory harmonization, "[t]he use of any prescription drug entails a risk of life-threatening adverse reactions. These risks will be compounded if decisions about safety and efficacy are delegated to . . . foreign governments."⁸²

Defenders of the FDA's current practice cite studies that show the potential dangers of early approval of new drugs in Europe. A report released by Public Citizen claims that the FDA's stringent safety and efficacy requirements have saved many lives by preventing dangerous drugs from reaching the U.S. market.⁸³ The report documented 56 drugs that had been approved for marketing in one or more European nations and then later withdrawn after causing adverse reactions in patients.⁸⁴

Given the FDA's generally positive record in protecting the public from pharmaceutical disasters, such safety concerns have validity. Indeed, the dominant status of American and European pharmaceutical companies in the world market raises the specter of excessive industry influence over any mutual recognition scheme. The FDA or the EMEA could conceivably engage in a competitive "race to the bottom" of the regulatory pool in an effort to assuage industry lobbyists or give favorable treatment to domestic manufacturers.

However, the assertion that swift approval of new drugs will cause some deaths or injuries is only half of the public health equation, because beneficial new drugs also save lives and reduce suffering due to illness. Moreover, an increase in mutuality or reciprocity with the EMEA avoids many of the substantial safety concerns associated with the more radical devolution of regulatory authority to private groups.⁸⁵ As a governmental agency, the EMEA would share with the FDA the fundamental regulatory goals of balancing public safety against the potential therapeutic gains from new drugs. Furthermore, if the FDA were able to show legitimate doubts about a new drug's safety, it could avoid reciprocal approval of a drug already certified by the EMEA.

C. *Demography and Culture*

Other problems arise from cultural and demographic differences between the United States and the European Community. Certain medical evidence suggests that different racial and ethnic groups experience different reactions to various pharmaceutical products, so that a

⁸² Letter from Sen. Edward Kennedy and Reps. John Dingell and Henry Waxman to FDA Commissioner David Kessler (Nov. 13, 1991), cited in Jordan, *supra* note 68, at 502.

⁸³ See *Study Says U.S. Has Better Barrier to Bad Drugs Than Europe*, WASH. POST, Feb. 3, 1995, at A9.

⁸⁴ See *id.*

⁸⁵ See *supra* p. 2015-16.

drug that is generally safe and effective in one population group might be less so in other racial or ethnic groups.⁸⁶ Without proper rules governing the acceptance of European clinical trials, the FDA might find itself without adequate indicia of safety and effectiveness for the ethnically and racially diverse American population.

Two factors mitigate this problem, however. First, Europe itself is rapidly becoming more ethnically and racially diverse as a result of recent immigration.⁸⁷ Presumably the EMEA will of necessity take this increasing diversity into account before approving a drug for the entire EC market. Second, under the scheme proposed in this Note, the FDA would have an opportunity to reject a new drug already approved in Europe. If the FDA were convinced that the European data on a particular new drug is inadequate to assess properly that compound's safety or effectiveness for all sectors of the U.S. population, the agency could deny recognition on that basis or require additional studies to assuage its concerns.

Cultural differences also confound efforts at regulatory mutuality between Europe and the United States. Governmental regulation of drugs that have beneficial therapeutic potential involves a societal weighing of risk and benefit. To a large extent, societal attitudes toward risk are culturally constructed, and they may vary widely between populations.⁸⁸ Because these societal attitudes are related to the particular social institutions and organization of a society,⁸⁹ the different historical development of public bodies in Europe and America may make problematic an interrelated drug regulatory scheme.

There is some evidence to suggest that American attitudes about risk are different from those in other countries. A study by Sheila Jasanoff revealed variances between citizens of Britain and the United States in their attitudes toward four different types of environmental risk.⁹⁰ Jasanoff found that "[i]n Britain, scientists and governmental decision makers are certain to recognize a risk only when there is persuasive evidence of actual harm . . . whereas in the United States a

⁸⁶ For instance, several studies have uncovered differences in the responses of blacks and whites to drugs designed to treat hypertension. See, e.g., Veterans Administration Cooperative Study Group on Antihypertensive Agents, *Comparison of Propranolol and Hydrochlorothiazide for the Initial Treatment of Hypertension*, 248(16) J.A.M.A. 1996, 2000 (1982) (finding that "blacks were more likely to respond to hydrochlorothiazide than propranolol," but finding that whites responded similarly to both drugs).

⁸⁷ See John Pomfret, *Europe's "Rio Grande" Floods with Refugees: Rich Nations Becoming Inundated By Millions Fleeing War, Poverty*, WASH. POST, July 11, 1993, at A1.

⁸⁸ See generally STEPHEN BREYER, *BREAKING THE VICIOUS CIRCLE: TOWARD EFFECTIVE RISK REGULATION* 33-39 (1993) (describing the inconsistent and often irrational perceptions of risk held by the American public).

⁸⁹ See MARY DOUGLAS & AARON WILDAVSKY, *RISK AND CULTURE* 9 (1982).

⁹⁰ See Sheila Jasanoff, *Cultural Aspects of Risk Assessment in Britain and the United States*, in *THE SOCIAL AND CULTURAL CONSTRUCTION OF RISK* 359, 385 (Branden B. Johnson and Vincent T. Covello eds., 1987).

risk may also be acknowledged where there is no direct proof of injury to the public.⁹¹ This cultural diversity of attitudes may be compounded in the realm of personal illness — especially terminal disease — where the very notion of “risk” becomes indeterminate and subjective. Finally, more identifiable cultural differences between the United States and the EC might arise with respect to moral attitudes about certain drug products, such as the European “abortion” drug RU-486⁹² or pharmaceuticals developed from the use of fetal tissue research or particularly intensive animal testing.

Concerns about different European and American attitudes toward risk, safety, and morality are relevant to any movement toward harmonization in drug regulation. However, like the demographic differences described above, such variances need not doom the entire scheme. The FDA and the EMEA would need to reach a general level of agreement on acceptable risk levels, but in particular instances of discord, the FDA would retain the final authority to show why it did not approve a particular new drug which passed EMEA scrutiny.

V. CONCLUSION

The firestorm of attention directed at the FDA’s drug approval process in recent months strongly suggests that *some* change will take place in the agency’s procedures. Whether these reforms will be truly effective or will instead be mere window-dressing remains to be seen, and largely depends on policymakers’ willingness to consider innovative and substantial proposals for reform. In this regard, radical deregulation that would eliminate the FDA’s pre-marketing approval authority over new drugs goes too far. Instead, a healthy dose of regulatory cooperation and competition with its new counterpart, the European Medicines Evaluation Agency, may be the best possible solution for the FDA.

⁹¹ *Id.*

⁹² For a general description of the controversy surrounding RU-486, see Carol Jouzaitis, *Abortion Pill Battle Surprises French Firm*, CHI. TRIB., Oct. 17, 1994, at C1.