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International Regulatory Harmonization: A New Era in Prescription Drug Approval

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NOTES

International Regulatory Harmonization: A New Era in Prescription Drug Approval

ABSTRACT

Critics of the Food and Drug Administration (FDA) have asserted that the agency's process of reviewing new drugs has long been laden with inefficiency and waste and, as a result, new drugs are not made available to consumers on a timely basis. This Note considers the veracity of this claim by examining the history of prescription drug regulation in the United States and the current procedure by which new drugs are reviewed. This Note also addresses the limited extent to which the FDA has interacted with its foreign counterparts in assessing the safety and efficacy of new drugs and the resultant difficulties caused by the FDA's isolationist policies. The Note discusses harmonization, a regulatory reform effort by the FDA and its counterparts in Japan and the European Community, under which pharmaceutical companies need to perform only one set of clinical tests on a new drug to satisfy the testing requirements imposed in the United States, Japan, and the European Community. The Note concludes by addressing the effect that harmonization, if implemented, will have on the major issues involved in the consideration of a new drug for approval, namely the time needed for approval, costs involved in the approval process, and the safety and efficacy of the new drug. The author states that harmonization is a conservative yet vital step in making needed drugs available to consumers in a timely manner and that the perceived weaknesses of harmonization are basically unfounded.

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I. INTRODUCTION

On October 11, 1988, AIDS protesters shut down the United States Food and Drug Administration (FDA) headquarters in Maryland by blocking entrances to the building, climbing atop doorways, and smashing windows.[1] Organizers of the protest cited as the impetus of their protest the lethargy of the FDA in reviewing new drugs with potential life-saving effects for AIDS patients.[2]

This incident is perhaps the most vivid display of criticism of the FDA's drug approval process which some critics perceive as a "notoriously slow, almost obstructionist, approach to testing experimental . . . drugs."[3] A recent study found that the average time needed to bring a new drug to the United States market is nearly ten years.[4] As Senator Hatch noted recently, "many [people] can't wait ten years for new

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1. Renee Loth, *AIDS Protesters Close FDA Headquarters,* BOSTON GLOBE, Oct. 12, 1988, at A1.

2. *Id.* The rally was organized by the ACT UP coalition, an AIDS activist group. *Id.* AIDS activists have become some of the most vocal opponents of the FDA drug approval process. *See, e.g.,* Marlene Cimons, *Panel Urges FDA to Allow New AIDS Drug on Market,* L.A. TIMES, July 20, 1991, at A1, A19; Malcolm Gladwell, *FDA Streamlining Approval Process for Cancer Drugs,* WASH. POST, June 4, 1991, at A21.

3. John K. Van de Kamp, *Van de Kamp and RU 486 Testing,* L.A. TIMES, Mar. 29, 1990, at B6. "[A]ccording to George Hitchings, co-winner of the 1988 Nobel Prize in medicine, FDA's five-year delay in approving the antibacterial drug Septra cost 80,000 lives." Sam Kazman, *Protected to Death: The FDA's Misbegotten AIDS Rules are Killing with Kindness,* WASH. POST, July 16, 1989, at B5. Another FDA "outrage" was its slowness in reviewing a drug (THA) which would provide effective treatment for 40% of those suffering from Alzheimer's disease. Malcolm S. Forbes, Jr., *Fact and Comment: (Low Fat) Bread and Circuses,* FORBES, July 8, 1991, at 23, 24. Critics have attacked the FDA on other grounds:

> The FDA must also change the way it handles the final set of tests for a new drug in which one control group uses a placebo, the other the drug itself. This raises a moral question: Shouldn't people with lethal or debilitating diseases take the real medicine? Over 80% of the drugs in this last phase ultimately get the green light. How would you like it if, facing death, you were given a useless placebo?

Id.

Critics have also challenged the FDA's resource priorities. For example, in 1991, the FDA attacked food company claims of freshness of their orange juice and their alleged mislabeling of products as being low in cholesterol. A critic of the FDA stated that "the real health-threatening abuses are not orange juice labels; they are the practices and procedures of [the FDA]." *Id.*

4. COUNCIL ON COMPETITIVENESS, IMPROVING THE NATION'S DRUG APPROVAL PROCESS 2 (1991) [hereinafter Drug Fact Sheet].

therapies."[5]

Many of the drugs mired in the FDA approval process already have received approval in other countries. Many seriously ill United States residents have decided to travel abroad to obtain these drugs, while others have had these unapproved drugs smuggled into the United States.[6] Some people have taken their own lives rather than suffer while the drugs await approval.[7]

Even state governments have demonstrated their exasperation with FDA apathy. The Nevada state legislature granted marketing approval to a drug manufactured by a Nevada company that had failed to gain FDA approval.[8] More recently, the California state legislature created its own process for testing and approving new drugs.[9] The "shadow FDA"[10] created in California has been praised for increasing the availability of certain drugs and for raising public awareness of the lethargy that allegedly pervades the FDA drug approval process.[11]

The purpose of this Note is to explore the circumstances that have created the controversy surrounding the FDA and to evaluate a recently announced transnational approach to drug approval which the FDA has asserted will expedite drug approval. This Note identifies the various stages of the FDA drug approval process and the factors that have lengthened that process. This Note examines the alleged "drug lag" in marketing approval in the United States and how the FDA has responded to this lag over the years. This Note also considers how international harmonization will affect the drug approval process, specifically in terms of the time needed for approval of new drugs, the costs incurred in the manufacture and purchase of new drugs, and the quality of the re-

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5. Orrin Hatch, *Let's Act to Bolster FDA's Authority to Speed Approval of Life-Saving Drugs, Writes Hatch,* ROLL CALL, Sept. 12, 1991 (Policy Briefing No. 31).

6. *See* Kazman, *supra* note 3.

7. *See, e.g.*, Michael L. Millenson, *Drug Test Ends, and Agony Returns,* CHI. TRIB., Oct. 31, 1991, at 1.

8. Larry Kramer, *Gambling With the FDA in Nevada: Businessman Wins State Approval to Market Drug; State Approves Drug that Claims to Help the Elderly,* WASH. POST, Nov. 13, 1977, at Fl. A New York businessman, Marvin Kratter, bought a failing drug company and won approval of the drug Gerovital in Nevada. The FDA admitted that this intrastate approval is legal so long as all aspects of production, distribution and consumption of the drug are kept within the state's borders. *Id.*

9. *See* Van de Kamp, *supra* note 3. For further discussion of this legislation, see Philip J. Hilts, *Seeking to Bypass Delays, State to Test AIDS Drugs,* WASH. POST, Oct. 1, 1987, at A3.

10. Michael Specter, *A Clash of Caution and Urgency: FDA's Drug-Approval Challenge,* WASH. POST, Oct. 26, 1987, at A11.

11. Van de Kamp, *supra* note 3.

view process for new drugs. Finally, this Note recommends changes in the FDA's drug approval process that will allow the benefits of harmonization to be realized.

II. GOVERNMENTAL REGULATION OF DRUG APPROVAL IN THE UNITED STATES

A. *History*

1. Pure Food and Drugs Act of 1906

The federal government's first significant attempt to regulate pharmaceutical distribution occurred in 1906 when Congress passed the Pure Food and Drugs Act (1906 Act).[12] The 1906 Act is regarded as a "landmark in the modern control of drugs."[13] The primary effect of the 1906 Act was to dictate labeling requirements for any substance used to treat disease.[14] The central purpose of this legislation was to assure consumers of the identity of the article purchased, not to ensure its usefulness in treating disease.[15]

Despite the significant increase in governmental control after passage of the 1906 Act, the effectiveness of the 1906 Act as a vehicle for regulation of new drugs was limited. The Supreme Court stated that Congress, in prohibiting labels that are "false or misleading in any particular," intended to make unlawful any false statements about the contents of new drugs.[16] Thus, false statements about a drug's strength, quality, or purity violated the 1906 Act, whereas false statements about a drug's therapeutic effects did not violate the 1906 Act.[17]

Congress responded by adding to the 1906 Act the requirement that labels must not contain "any statement . . . regarding the curative or therapeutic effect . . . which is false and fraudulent."[18] The regulatory impact of the amendment was minimal because proving the falsity of

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12. Pure Food and Drugs Act of 1906, ch. 3915, §§ 1-13, 34 Stat. 768, *repealed by* Federal Food, Drug, and Cosmetic Act of 1938, ch. 675, § 902(a), 52 Stat. 1040, 1059 (codified as amended at 21 U.S.C. § 301 (1988)).

13. *See* WILLIAM M. WARDELL & LOUIS LASAGNA, REGULATION AND DRUG DEVELOPMENT 6 (1975).

14. *Id.*

15. PETER TEMIN, TAKING YOUR MEDICINE: DRUG REGULATION IN THE UNITED STATES 33 (1980).

16. United States v. Johnson, 221 U.S. 488 (1911). The Court held that a shipper's claim that a drug was a cancer remedy was not a violation of the 1906 Act. *Id.*

17. *See* TEMIN, *supra* note 15, at 33.

18. Sherley Amendment, Pub. L. No. 62-301, 37 Stat. 416, 417 (1912) (repealed 1938).

therapeutic claims was extremely difficult.[19] Further limiting the value of the amendment was the continued burden on aggrieved parties to prove that a drug sponsor fraudulently concealed its knowledge that its therapeutic claims were false.[20]

2. The Food, Drug, and Cosmetic Act of 1938

The 1906 Act outlawed fraud in an effort to prevent financial loss to consumers; it did not protect consumers against unsafe drugs.[21] Demand for governmental scrutiny of a drug's safety significantly increased in 1937, in the wake of the "Elixir Sulfanilamide" tragedy, in which at least seventy-three people died as a result of taking a drug prepared by a small Tennessee pharmaceutical manufacturer.[22]

In June 1938, Congress reacted to the "Elixir Sulfanilamide" incident by passing the Federal Food, Drug and Cosmetic Act of 1938 (1938 Act)[23] which, as amended, is the law today.[24] The 1938 Act requires drug sponsors to file an application for marketing approval of a new drug.[25] The FDA then has the option to test the drug for its safety in

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19. TEMIN, *supra* note 15, at 33-34.

20. *Id.* For example, the sponsor simply could plead ignorance regarding the drug's therapeutic effects. *Id.* at 34. For a more detailed analysis of the thrust of the federal government's drug approval policy during the early part of the 20th Century, see generally *id.* at 35-37.

21. *Id.* at 44.

22. *See* RICHARD A. MERRILL & PETER B. HUTT, FOOD AND DRUG LAW 369 (1980). "Elixir Sulfanilamide" was prepared by S.E. Massengil Co. to make a valuable new drug, sulfanilamide, available in liquid form. The drug sponsor tested the elixir only on the basis of its appearance, flavor, and fragrance. Any animal testing or examination of published literature would have revealed the lethal character of the solvent used to prepare the elixir. *Id.*

23. Federal Food, Drug and Cosmetic Act of 1938, ch. 675, § 501, 52 Stat. 1040, 1049 (codified as amended at 21 U.S.C. § 351 (1988)) [hereinafter 1938 Act].

For a comparison of the coverage of the 1938 Act and the 1906 Act, see TEMIN, *supra* note 15, at 43.

While the Sulfanilamide tragedy is regarded as the single most important event leading to passage of the 1938 Act, commentators have suggested that the 1938 Act was based more on the economic conditions of the time. Temin, for example, attributes passage of the 1938 Act to: (1) policymakers' view that the Great Depression proved that the market economy lacked the ability to protect people from economic and noneconomic problems, and (2) the view that consumers were incapable of making drug purchasing decisions without governmental regulation. *Id.* at 54-55.

24. TEMIN, *supra* note 15, at 43.

25. 1938 Act, 21 U.S.C. § 355 (1988); *see also* WARDELL & LASAGNA, *supra* note 13, at 16-17. Under the original 1938 Act, the FDA did not exert any power until a manufacturer sought marketing approval. Up to the marketing approval stage, the spon-

human consumption.[26] The government's failure to respond to the application results in approval of the application, and the sponsor can proceed to market the drug.[27] The 1938 Act is significant in that it provides the government with the power to decide which drugs are legally marketable, even in cases which do not involve fraud or misrepresentation.[28]

3. Drug Amendments of 1962

No new reforms in drug approval in the United States occurred until after the thalidomide drug tragedy in Europe in the 1960s.[29] "[H]urriedly in a crisis atmosphere,"[30] Congress enacted the Drug Amendments of 1962 (1962 Amendments).[31] The 1962 Amendments greatly expand the scientific, technical, and administrative requirements for obtaining drug approval.[32]

The 1962 Amendments require, for the first time, drug sponsors to prove that new drugs are effective as well as safe for their intended use.[33] The 1962 Amendments require evidence of a new drug's effective-

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sor would decide on the types of clinical tests and the extent to which such tests would be performed. In filing its application, the drug sponsor would decide what data concerning toxic reactions would be submitted to the FDA. *Id.*

26. 1938 Act, 21 U.S.C. § 355 (1988); *see also* WARDELL & LASAGNA, *supra* note 13, at 8 (discussing how control over new drugs was viewed in the 1938 Act).

27. 1938 Act, 21 U.S.C. § 255(c) (1988). *See also* TEMIN, *supra* note 15, at 44.

28. *See* TEMIN, *supra* note 15, at 44.

29. Prescribed as an antidote to morning sickness in pregnant women, thalidomide caused deformities in thousands of babies in Europe. *See* Harvey Teff, *Drug Approval in England and the United States*, 33 AM. J. COMP. L. 567, 567 (1985).

30. MERRILL & HUTT, *supra* note 22, at 372.

31. Pub. L. No. 87-781, § 102(b), 76 Stat. 780 (codified as amended at 21 U.S.C. § 355(b) (1988)) [hereinafter 1962 Amendments].

32. *See* Kleinfeld et al., *Human Drug Regulation: Comprehensiveness Breeds Complexity, in* SEVENTY-FIFTH ANNIVERSARY COMMEMORATIVE VOLUME OF FOOD AND DRUG LAW 242, 245 (1984).

33. *See* 1962 Amendments, 21 U.S.C. § 355(b) (1988). The 1962 Amendments inserted the phrase "and whether such drug is effective in use" after the phrase "is safe for use." *Id. See* Henry G. Grabowski, *Regulation and the International Diffusion of Pharmaceuticals, in* THE INTERNATIONAL SUPPLY OF MEDICINES: IMPLICATIONS OF U.S. REGULATORY REFORM 5, 7-8 (Robert B. Helms ed., 1980) (discussing the characteristics of the 1962 Amendments). Under the original 1938 Act, testing for a drug's efficacy, or effectiveness, was largely beyond the scope of the FDA's premarketing review. *See* MERRILL & HUTT, *supra* note 22, at 370.

Because the 1962 Amendments arose partially out of the European thalidomide tragedy, it is interesting to note that the 1962 legislation did not bolster safety standards, only efficacy standards. *See* Jim Dickinson, *Is FDA a Major Failure?*, MED. MARKETING & MEDIA, Oct. 1990, at 4.

ness to be collected through "adequate and well controlled investigations, including clinical investigations," conducted by experts.[34] The 1962 Amendments also require drug sponsors to gain FDA approval before commencing clinical tests.[35] Before enactment of the 1962 Amendments, the FDA was not involved in the regulation of new drugs until after the sponsor of clinical tests had sought marketing approval.[36]

The 1962 Amendments enhance the FDA's power at the marketing approval stage. Instead of providing automatic approval for those new drugs that the FDA does not expressly disapprove, the 1962 Amendments require affirmative FDA approval prior to the marketing of new drugs.[37]

B. *Drug Approval Process*

The 1938 Act provides two routes by which a new drug[38] can gain approval for marketing in interstate commerce: (1) the drug must be one that the 1962 Amendments exempted from the operation of the 1938 Act[39] or (2) the drug must gain FDA approval under the New Drug Application (NDA) procedures.[40] The latter method applies to all new drugs, but the 1938 Act provides a relaxed process for certain types of

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34. 1962 Amendments, 21 U.S.C. § 355(b) (1988); *see also* Grabowski, *supra* note 33, at 7 (This requirement "is generally regarded as a major factor in producing much longer and costlier development periods for new drugs in the post-1962 period.").

The FDA will reject an application if "there is a lack of substantial evidence that the drug will have the effect it purports . . . to have." 21 U.S.C. § 355(e) (1988). This "substantial evidence" standard has been the subject of litigation. *See, e.g.*, Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. 609 (1973).

The FDA also has the power to withdraw approval of a drug based on new information which shows that efficacy is lacking. 21 U.S.C. § 355(e) (1988).

35. 1962 Amendments, 21 U.S.C. § 355(b) (1988); *see also* Grabowski, *supra* note 33, at 7.

36. *See* Grabowski, *supra* note 33, at 7.

37. 1962 Amendments, 21 U.S.C. § 355(a) (1988); *see also* WARDELL & LASAGNA, *supra* note 13, at 24 (discussing the elimination of the automatic approval of a new drug if the drug not expressly disapproved).

After the 1962 Amendments, FDA took a more significant role in the drug approval process. The general wording of the statute gave FDA substantial latitude in promulgating regulations. *See id.* at 19.

38. A "new drug" is defined broadly at 21 U.S.C. § 321 (1988).

39. JAMES R. NIELSEN, HANDBOOK OF FEDERAL DRUG LAW 13 (1986). If a drug was generally recognized as being safe and effective at the time the 1962 Amendments became effective, the drug was exempted from operation of the Amendments. *Id.*

40. Id. *See* 21 U.S.C. § 355(a), (b) (1988) (stating that an application must be filed and approved before any new drug may be introduced into interstate commerce).

drugs.[41] The approval process includes pre-clinical testing, IND stage testing, NDA stage testing, and post-marketing surveillance.

1. Pre-Clinical Testing

In pre-clinical testing, which takes an average of eighteen months,[42] the drug sponsor conducts initial investigations of the drug through tests on laboratory animals.[43] The purpose of the tests is "to identify the nature of the chemical entity being investigated and to establish sufficient evidence" of the drug's toxicity "to determine if it is reasonably safe for human beings in preliminary clinical investigations."[44]

2. IND Stage

If, after conducting pre-clinical tests, the drug sponsor concludes that the new drug shows a high degree of promise in treating a specific disease and the studies indicate that clinical trials would be safe, the sponsor files a Notice for Claimed Investigational Exemption for a New Drug (IND) with the FDA.[45] In its application, the sponsor reports the results of pre-clinical testing and discloses how the drug is made.[46]

After submitting the IND application, the drug sponsor must wait thirty days to allow the FDA to review the application.[47] If the FDA notifies the drug sponsor that studies may not commence, the IND does not take effect.[48] If the FDA responds favorably or does not respond within this thirty-day period, the sponsor may begin clinical investigations pursuant to the standards set forth in the IND application and in

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41. *See infra* notes 58 and 62.

42. Drug Fact Sheet, *supra* note 4, at 2.

43. *See* 21 C.F.R. § 312.23(a)(8) (1992) (mandating disclosure of pharmacological and toxicological effects of the proposed new drug on laboratory animals). *See generally* Kleinfeld, et al., *supra* note 32, at 245 (discussing the nature of animal testing).

44. *See* 21 C.F.R. § 312.22 (1992) (general principles of the IND submission); *see also* Kleinfeld et al., *supra* note 32, at 245.

45. *See* 21 U.S.C. § 355(i) (1988) (directing the FDA to promulgate regulations pertaining to investigational exemptions); 21 C.F.R. §§ 312.3(b), 312.20 (1992).

46. *Can the FDA Meet Its Critics' Demands?*, PHARMACEUTICAL BUS. NEWS (London), Mar. 31, 1989. For a complete listing of the required contents and format of the Notice, see 21 C.F.R. § 312.23 (1992).

Specific FDA requirements on animal toxicology have largely eliminated clinical studies preceded only by minimal animal testing. *See* WARDELL & LASAGNA, *supra* note 13, at 19.

47. 21 C.F.R. § 312.40(b)(l) (1992).

48. *Id.* Any IND is subject to a "clinical hold" under 21 C.F.R. § 312.42 (1992).

agency regulations.[49]

The IND stage includes three phases of clinical investigations. Phase I begins with initial tests of the new drug on human beings.[50] Clinicians administer the drug in low doses to up to 100 healthy volunteers.[51] The purpose of this phase is to determine the new drug's toxicity and obtain other pharmacological information.[52] The average length of time for Phase I is six months.[53]

Phase II is an extension of Phase I. In this phase, the primary consideration is whether the drug is effective.[54] Clinicians conduct controlled studies, usually involving several hundred volunteers who have contracted the disease that the drug sponsor intends the drug to treat.[55] The studies clarify dosage requirements, confirm the new drug's therapeutic effects, and compare the new drug's effects with those of existing drugs.[56] Phase II lasts, on average, eighteen months.[57]

Phase III is the longest and most extensive phase of clinical testing. It also is the most time-consuming part of the entire approval process, lasting an average of three years.[58] This phase begins only if data from the first two phases offer reasonable assurance that the drug is effective and safe and that the potential benefits of the drug outweigh the risks of a larger clinical trial.[59]

In this phase, physicians administer clinical tests to numerous volunteers.[60] The purpose of this phase is to study the circumstances under

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49. 21 C.F.R. §§ 312.40(b), 312.50 (1992) (identifying general responsibilities of drug sponsors).

50. 21 C.F.R. § 312.21(a) (1992).

51. *Id.*

52. Specific other pharmacological information gathered on the new drug includes drug metabolism, absorption and elimination, and preferred route of administration. *Id.* *See also* Kleinfeld et al., *supra* note 32, at 245 (discussing Phase I).

53. Drug Fact Sheet, *supra* note 4, at 2.

54. *See* 21 C.F.R. § 312.21(b) (1992).

55. *See id.*

56. *Id; see also* MERRILL & HUTT, *supra* note 22, at 405 (discussing Phase II).

57. Drug Fact Sheet, *supra* note 4, at 2.

58. *Id.* A set of temporary procedures promulgated by the FDA allow marketing of certain drugs to treat life-threatening illnesses without Phase III clinical trials. However, "[w]hile the content and spirit of the FDA's message are commendable, the dogmatic application of identical safety and efficacy standards to all drugs severely undercuts the message." John P. Dillman, Note, *Prescription Drug Approval and Terminal Diseases: Desperate Times Require Desperate Measures*, 44 VAND. L. REV. 925, 942 (1991).

59. 21 C.F.R. § 312(c) (1992).

60. *Id.*; *see also* Specter, *supra* note 10, at All (discussing the nature of Phase III). The number of volunteers can range from 150 to 3,000. *Id.*

which physicians prescribe the drug for their patients.[61] This broad clinical trial allows the sponsor and the FDA to assess the safety of the drug's optimum dosage schedule and its effectiveness in the diagnosis and treatment of patients.[62]

The FDA may terminate clinical testing at any phase if the tests do not meet the conditions of the IND exemption.[63] The IND exemption requires the drug sponsor to maintain records of shipments of drugs to investigators, to monitor the progress of investigations, and to report to the FDA and all clinical investigators any adverse reactions.[64] The sponsor may be required to terminate the investigation if substantial doubt arises about the safety or efficacy of the drug.[65]

3. NDA Stage

After successful completion of the three phases of the IND stage, the drug sponsor must file a New Drug Application (NDA) with the FDA.[66] The NDA "has become the principal regulatory device for the control of drugs in the United States."[67] To show that the drug is safe the NDA must include data derived from "adequate tests by all methods reasonably applicable."[68] It also must include "substantial evidence" that the drug is effective for use under the conditions described in its labeling.[69]

The information required in an NDA is extensive. An NDA requires a drug sponsor to present an exhaustive review of virtually all the information it possesses about the drug.[70] The required information includes references to any INDs affecting the drug. Evaluations of safety and ef-

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61. *See* 21 C.F.R. § 312.21(c) (1992); MERRILL & HUTT, *supra* note 22, at 405.

62. C.F.R. § 312.21(c) (1992). The FDA has developed a special accelerated IND process, known as "Treatment IND," for proposed AIDS therapies. *See* 21 C.F.R. § 312.34(b) (1992).

63. *See* 21 C.F.R. § 312.44(a) (1992) (describing the FDA's power to terminate the IND process). For a listing of specific grounds for termination at each of the three phases of the IND process, see 21 C.F.R. § 312.44(b) (1992).

64. 21 C.F.R. §§ 312.50, 312.56, 312.57 (1992).

65. 21 C.F.R. § 312.44(vii) (1992) (describing the FDA's power to terminate an IND if the drug sponsor fails to investigate and to inform the FDA promptly of serious and unexpected adverse experiences as required by 21 C.F.R. § 312.32 (1992)).

66. *See* 21 U.S.C. § 355(a)-(b) (1988). *See generally* NIELSEN, *supra* note 39, at 15-17 (discussing the NDA process).

67. NIELSEN, *supra* note 39, at 15.

68. 21 U.S.C. § 355(d)(1) (1988).

69. 21 U.S.C. § 355(d)(5) (1988); *see also* Kleinfeld et al., *supra* note 32, at 246 (discussing NDA process standards).

70. NIELSEN, *supra* note 39, at 15.

fectiveness, methods of manufacture, chemistry, lists of investigators and their full reports, proposed labeling of the drug, and proposed instructions are required.[71] Preparing an NDA for submission to the FDA takes an average of eight months.[72]

The FDA staff, representing various scientific disciplines, including medicine, pharmacology, and chemistry, reviews the data in the application.[73] The FDA staff assigns the NDA to a division within the FDA's National Center for Drugs and Biologics.[74] Ultimately, the division head assigns the drug to a group within the division. The group leader assigns work to staff personnel and establishes priorities for the group's consideration of NDAs.[75]

Once a sponsor files an NDA, the FDA technically has 180 days to approve or disapprove the proposed drug.[76] The FDA has interpreted the term "filed" narrowly, however, stating that an NDA will not be deemed filed until it is "approvable."[77] If the FDA ultimately rejects an NDA, the sponsor may request a second FDA review. If the FDA re-

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71. *Id.* at 15-16.

72. Drug Fact Sheet, *supra* note 4, at 2. In 1982, the FDA announced a permanent reform known as an "NDA rewrite," which was intended to streamline the application format, expedite the appeals process, and provide for more thorough reporting of post-marketing problems. At the time this reform was announced, an average NDA was one hundred thousand pages. The benefits of this reform have been dubious. *See* Dillman, *supra* note 58, at 940-41.

73. *See* Kleinfeld et al., *supra* note 32, at 246 (discussing the interaction of personnel from the respective disciplines).

74. *Id.* The FDA's six review divisions are cardio-renal, neuropharmacological, metabolism-endocrine, anti-infective, oncology-radiopharmaceutical, and surgical-dental. *FDA Monitors Drug Evolution After Private Sector's Creation*, CHI. TRIB., Nov. 16, 1986, at 28 [hereinafter *FDA Monitors*].

75. *See* Kleinfeld et al., *supra* note 32, at 246.

76. 21 U.S.C. § 355(c) (1982), 21 C.F.R. § 314.100(a) (1992). Within 180 days, the FDA will review the NDA and send the applicant an "approval" letter under 21 C.F.R. § 314.105 (1992), an "approvable" letter under 21 C.F.R. § 314.110 (1992), or a "not-approvable" letter under 21 C.F.R. § 314.120 (1992).

77. *See* Kleinfeld et al., *supra* note 32, at 246-47; 21 C.F.R. § 314.125 (1992).

The FDA's definition of "approvable" is unclear. Still, the FDA's policy in this regard has been upheld in court. *See, e.g.*, Newport Pharmaceuticals Int'l, Inc. v. Schweiker, Food Drug Cosm. L. Rep. (CCH) ¶38,148 at 38,878 (D.D.C. Dec. 2, 1981). This policy gives the agency broad discretion in determining the length of time it will use to act on an NDA. Kleinfeld et al., *supra* note 32, at 247.

In addition to criticism of this discretionary policy, it has been argued that sponsors regularly fail to receive substantial feedback on their application until the 180 day period has almost expired. WARDELL & LASAGNA, *supra* note 13, at 24. Further, even if the FDA has admitted that the NDA is "approvable", it may still request further delay, which the sponsor has no real power to contest. *Id.*

jects the drug again, the sponsor may request a judicial hearing.[78] Due to the FDA's extensive discretion, no drug sponsor has ever won judicial reversal of the FDA's refusal to approve a drug.[79] If the FDA approves an NDA, the sponsor must file periodic reports concerning the drug.[80] The FDA may condition approval upon the sponsor's willingness to undertake post-marketing approval studies.[81] The FDA's NDA review process takes an average of two and one-half years.[82]

4. Post-Marketing Surveillance

The 1938 Act does not specifically require drug sponsors to conduct post-marketing surveillance studies.[83] Also known as Phase IV testing, these studies have become routine through agency practice and industry acquiescence.[84] The goal of post-marketing surveillance studies is to obtain additional information on a drug's safety and efficacy.[85]

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78. *See* 21 C.F.R. § 314.120(c) (1992); 21 C.F.R. § 314.200(a) (1992).

No hearing is required unless evidence is presented that justifies the need for a hearing. Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. 609 (1973). If a hearing is denied, or if granted but the Commissioner of Food and Drugs agrees with the FDA that approval is not warranted, the sponsor may appeal to a United States Court of Appeals. 21 U.S.C. § 355(h) (1988); 21 C.F.R. § 314.235 (1992).

79. *See* MERRILL & HUTT, *supra* note 22, at 415 (discussing drug sponsors' lack of success in gaining judicial reversal of FDA decisions not to approve a drug). *See also* Ubiotica Corp. v. FDA, 427 F.2d 376 (6th Cir. 1970) (taking deferential stance on FDA's decision not to approve a new drug).

80. 21 U.S.C. § 355(k) (1988).

81. *See* Kleinfeld et al., *supra* note 32, at 247 ("If an NDA is approved, the sponsor must maintain records and make periodic reports to the agency concerning the drug. Additionally, as a condition of approval it may be required to undertake Phase IV studies."). For an analysis of Phase IV requirements, see *infra* notes 83-85 and accompanying text.

82. Drug Fact Sheet, *supra* note 4, at 2 (The "FDA Approval Process" lasts 30 months on average).

83. *See generally* Marion J. Finkel, *Phase IV Testing: FDA Viewpoint and Expectations*, 33 FOOD DRUG COSM. L.J. 181 (1978). According to Finkel, the FDA's authority to require Phase IV testing is questionable. He recognizes the tension inherent in Phase IV testing. The FDA may be exercising authority that it does not rightfully possess; however, by exercising such authority, the FDA is willing to grant faster approval at the NDA stage than it would if Phase IV testing was unavailable. *Id.* at 183-84.

84. Kleinfeld et al., *supra* note 32, at 271. *See generally* 21 C.F.R. § 310.303-310.305 (1992) (regulations identifying specific reports to be filed over a span of many years as a condition to approval).

85. *See* Finkel, *supra* note 83, at 181. *See generally* Dillman, supra note 58, at 940-47 (analyzing recent FDA reforms).

C. *Criticisms of the United States Drug Approval Process*

Since the passage of the 1962 Amendments, the time required to gain approval for new drugs has risen sharply. In the early 1960s, a drug sponsor needed three to four years from pre-clinical testing through the NDA process to gain approval for new drugs.[86] By the mid-1970s, approval time had increased to seven years.[87] Today, the average time needed for approval is almost ten years.[88] Over the same period, the cost of developing new drugs has also increased dramatically. In the early 1960s, drug sponsors spent several million dollars in the review process; by the mid-1970s, the average cost was 50 million dollars.[89] Today, the cost exceeds 230 million dollars.[90]

While a number of factors contribute to these problems, the focus of criticism has been on the FDA and the statutory parameters within which it operates.[91] Drug development is tied inextricably to FDA regulation:

> [T]he present scheme for regulating drugs for human use is . . . pervasive; the regulatory framework covers every aspect of human drug products commencing with early laboratory research efforts, through clinical testing, to the critical decision on marketing approval. Regulation affects the manufacturing, promotion, and distribution of a drug and even its ultimate administration to and use by a patient. Each significant activity related to human drugs is governed by . . . regulatory requirements and, in many cases, is subject to proposed new regulations or suggested proposals to tighten, loosen, modify, or fine-tune the system.[92]

Because of the FDA's central role in drug approval, critics lay much of the blame for marketing delays and spiraling costs on the FDA and the statutory authority which grants the FDA its power.[93] The following discussion examines some of the most commonly cited factors that con-

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86. Grabowski, *supra* note 33, at 8. The time includes pre-clinical testing through NDA testing and approval by the FDA. *Id.*

87. *Id.*

88. Drug Fact Sheet, *supra* note 4, at 2.

89. Grabowski, *supra* note 33, at 8.

90. Paul Abrahams, *A Tricky Balancing Act for Regulators*, FIN. TIMES (London), Nov. 15, 1991, § I, at 19 (quoting a spokesperson of the Pharmaceutical Manufacturers Association of America).

91. *See, e.g.*, Kazman, *supra* note 3, at B5; Loth, *supra* note 1, at A1.

92. Kleinfeld et al., *supra* note 32, at 242.

93. *See, e.g.*, Louis Lasagna, *Promising New Drugs Deserve Faster Approval*, L.A. TIMES, Oct. 19, 1989, at B7 ("What is wrong with the FDA? Compared to the drug regulatory agencies of other countries, it is huge.").

tribute to the significant time and costs involved in gaining marketing approval.

1. Statutory Factors

Critics have charged that the 1962 Amendments are primarily responsible for the increase in time and costs required to gain FDA approval.[94] Several commentators have argued that the 1962 Amendments' proof of efficacy and clinical testing requirements are so stringent and have imposed such high costs on the drug development process that drug companies are reluctant to develop new drugs.[95] One commentator has suggested that a less costly statutory scheme may be needed to supplant the 1962 Amendments entirely.[96]

2. Factors Within the FDA

a. Failure to Adhere to Statute

Critics have argued that the FDA has interpreted improperly its statutory mandate.[97] As discussed above, although the FDA has 180 days to approve a filed NDA,[98] the FDA has interpreted the term "filed" to impose no duty on the FDA until it deems the sponsor's NDA "approvable."[99] One court had upheld this reading of the statute.[100] Several commentators, however, have argued that the FDA's use of up to three years to act on an NDA, when 180 days is the ostensible statutory limit, constitutes a clear violation of congressional intent.[101]

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94. *See* WARDELL & LASAGNA, *supra* note 13, at 47 ("It is now clear that the cost of developing a new chemical entity to the stage of NDA approval has [multiplied] since the 1962 amendments . . . and that the amendments are responsible for at least a substantial fraction of this increase."). *See generally* Henry G. Grabowski et al., *Estimating the Effects of Regulation on Innovation: An International Comparative Analysis of the Pharmaceutical Industry*, 21 J.L. & ECON. 133 (1978).

95. *See, e.g.*, WARDELL & LASAGNA, *supra* note 13, at 47.

96. *Id.*

97. *See, e.g.*, Gladwell, *supra* note 2, at A21 ("[A] problem . . . has plagued the [FDA] for the last 20 years: how to cut the time it takes FDA reviewers to decide whether to approve a drug. By law, this decision is supposed to take six months. But in the 1960s and 1970s, drug applications took an average of two years to get out of the FDA. By the 1980s that average had reached three years.").

98. 21 U.S.C. § 355(c) (1988); 21 C.F.R. § 314.100(a) (1992).

99. *See* Kleinfeld et al., *supra* note 32, at 246-47.

100. *Id.*

101. *See* Gladwell, *supra* note 2, at A21; *FDA Said to Be Slow to OK New Drugs*, FACTS ON FILE WORLD NEWS DIG., July 27, 1979, at 572 B2 (discussing the General Accounting Office's criticisms of the FDA).

b. Politics

Critics of the FDA also contend that the drug approval process lacks a quick and impartial mechanism for "judging who is right and who is wrong when a sponsor and the FDA are at loggerheads."[102] Drug companies, therefore, are hesitant to challenge the FDA's practices in court because they fear retaliation in the FDA's consideration of future filings.[103] Critics charge that if the FDA evaluated new drugs solely on their scientific and therapeutic merits, the drug approval process would be much more rapid.[104] Instead, the FDA allows quarrels with manufacturers and anticipated controversies over the marketing of new drugs to delay its consideration of new drugs.[105]

c. Insufficient Funding, Unqualified Personnel, and Bureaucracy

Major problems at the FDA are evident to visitors upon entering FDA headquarters in Maryland: "[It] is cheerless and inadequate in space, wiring and temperature control. These conditions and low pay scales discourage top-notch applicants for staff positions, and many senior posts are unfilled."[106]

Not surprisingly, the FDA's inability to attract high quality personnel has had a negative impact on FDA operations. A government-appointed committee that studied the FDA concluded that the lack of qualified personnel in the agency is a major problem.[107] The committee found that

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102. Lasagna, *supra* note 93, at B7. The FDA's political power is evidenced by the absence of any applications being filed in the United States for the French abortion pill, RU-486. Former California Attorney General John Van de Kamp attributed the lack of applications to "non-medical political pressure." Van de Kamp further asserted that application to the FDA is unlikely until there is a "positive regulatory climate which both encourages applications and promises decisions made on medical merits, rather than political pressure." Van de Kamp, *supra* note 3, at B6. Van de Kamp has proposed state testing and licensing for the abortion pill, RU-486. *Id.* RU-486 continues to create controversy. Recently, the FDA ordered the abortion pills to be seized from a pregnant California woman who had purchased the pills in France. The Supreme Court upheld the FDA's power to order this seizure. Benten v. Kessler, 112 S.Ct. 2929 (1992). About two weeks after this ruling, the FDA approved use of the drug by a brain cancer patient who told Congress that RU-486 might prolong his life. *See Cancer Patient Gets OK to Use RU-486*, S.F. EXAMINER, July 30, 1992.

103. Lasagna, *supra* note 93, at B7.

104. *See* Van de Kamp, *supra* note 3, at B6.

105. *Id.*

106. Lasagna, *supra* note 93, at B7.

107. Carol Griffee, *Dream Buster: Hopes for a Biotechnology Corridor Dying Due to New Federal Mandates at* NCTR, ARK. BUS., July 22, 1991, § 1, at 18. Health and Human Services Secretary Sullivan appointed the 15 member committee in March of

the FDA no longer has the scientific ability to evaluate new drugs or to stay abreast of "the revolutionary advances occurring in the biological and medical sciences."[108]

One critic has accused the leadership at the FDA of engendering a bureaucratic atmosphere by demanding duplicative levels of review that do not improve the quality of the review process.[109] In proposing new legislation that would require faster approval of new drugs, Senator Hatch has said there must be a "change in the [FDA's] review process so that it is more compatible with emerging scientific developments . . . and utilize[s] new clinical and laboratory methods to access drugs' efficacy more quickly."[110]

d. Systemic Bias Against Approval

Studies of regulatory agencies such as the FDA show that their reward structures encourage employees to perform their tasks cautiously, possibly with excessive caution.[111] Milton Friedman, a noted economist, explains this bias:

> The reason is very simple—no Food and Drug administrator has ever been pilloried for not approving a drug which was potentially capable of saving many lives. Any Food and Drug administrator is bound to be pilloried for making the other mistake, namely, approving a drug which turns out to be harmful.[112]

Consequently, FDA personnel have a natural bias to withhold new, potentially valuable, drugs from the market.[113] This bias is hidden but has very serious costs.[114] One commentator suggests that "[w]ithholding ef-

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1990. A former FDA Commissioner, Dr. Charles C. Edwards, was the chairman. *Id.*

108. *Id.*

109. *See* Gladwell, *supra* note 2, at A21; Lasagna, *supra* note 93, at B7 ("[T]he agency is raked over the coals for serving the public poorly, mostly through bureaucratic foot dragging."). For a well-reasoned viewpoint that the FDA should not bear the blame for its problems, see Dickinson, *supra* note 33, at 4 (The current problems are not FDA's fault. "And whoever's fault it is, we're not likely to get far by carrying on about it. . . . As with any run-down, abused resource, it will take a major investment now to repair the drug review process.").

110. Hatch, *supra* note 5.

111. *See generally* Robert B. Helms, *Preface* to THE INTERNATIONAL SUPPLY OF MEDICINES: IMPLICATIONS OF U.S. REGULATORY REFORM, *supra* note 33; SAM PELZMAN, REGULATION OF PHARMACEUTICAL INNOVATION (1974); WILLIAM A. NISKANEN, JR., BUREAUCRACY AND REPRESENTATIVE GOVERNMENT (1971).

112. Kramer, *supra* note 8, at F1 (quoting Milton Friedman).

113. *Id.*

114. *See Speedier Drugs*, THE ECONOMIST, Dec. 7, 1991, at 16; Abrahams, *supra*

fective new drugs from the public harms people [who do not have alternative means of therapy] just as surely as letting dangerous ones slip through."[115] Critics argue that the FDA must change the attitude of its personnel through a revamped reward structure which will foster a more efficient drug review process.[116]

III. A TRANSNATIONAL APPROACH TO DRUG APPROVAL: A VEHICLE FOR REFORM AT THE FDA?

A. *The Drug Approval Lag*

Many foreign and domestic observers believe that the FDA has one of the strictest regulatory philosophies of any drug regulatory agency.[117] Observers believe that this philosophy, coupled with the FDA's internal difficulties detailed in Part II, has produced a "drug approval lag" in the introduction of new drugs in the United States.[118]

The introduction dates of new chemical entities (NCEs)[119] in the United States and Europe show that since 1962, the United States has shifted from being a leader to lagging behind some European states in the introduction of new drugs.[120] A study conducted over a ten-year pe-

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note 90, § I, at 19; Lasagna, *supra* note 93, at B7.

One commentator considers the consequences of the FDA's carefulness:

> In . . . disease categories in which drug therapies are most urgently required, such as cancer and cardiovascular diseases, research will have to enter new fields. But, if we want 100 percent safety and security, then—by definition—we will be barred from entering these new fields. There, indeed, may well be an inherent logical contradiction between 100 percent safety and innovation, as well as between very strict regulation and innovation. In other words, excessively strict drug regulation may impede—and possibly is already impeding—the development of therapies for precisely those diseases.

Klaus von Grebmer, *Commentary, in* THE INTERNATIONAL SUPPLY OF MEDICINES: IMPLICATIONS OF U.S. REGULATORY REFORM, *supra* note 33, at 59, 61-62.

115. *Speedier Drugs*, *supra* note 114, at 16.

116. Abrahams, *supra* note 90, § I, at 19.

117. For a domestic view, see generally Grabowski, *supra* note 33, at 5-36. For a foreign view, see *Speedier Drugs*, *supra* note 114, at 16.

118. *See, e.g.*, Grabowski, *supra* note 33, at 35-36.

119. NCEs are drugs containing a single chemical formula not previously marketed. Virtually all significant therapeutic breakthroughs are NCEs. Sam Peltzman, *The Benefits and Costs of New Drug Regulation, in* REGULATING NEW DRUGS 113, 119 (Richard L. Landau, ed., 1973).

120. *See* Grabowski, *supra* note 33, at 35-36. This study by Grabowski further indicates that the lag is not confined to drugs with minor medical importance. It also includes drugs that the FDA itself considers to rank as therapeutically significant. The study "regulation has been a major factor contributing to this lag." The lag is particularly

riod showed that the FDA approved drugs it considered to be "therapeutically important" as much as five years after the United Kingdom approved the same drugs.[121] Another study showed that the two and one-half year NDA process in the United States is approximately one year longer than comparable processes in Europe and Japan.[122] Cross-cultural analyses suggest that drug regulatory agencies in Europe and Japan have achieved shorter approval times without sacrificing safety or efficacy standards in the process.[123]

The most obvious consequence of the drug lag has been the delayed access for United States residents to new drugs which are available elsewhere.[124] Another consequence has been a shifting of United States pharmaceutical companies' research and development activities to foreign sites.[125] The availability of faster governmental approval abroad has decreased the clinical research costs incurred in regulatory compliance and, therefore, new drugs enter foreign markets sooner than would be possible in the United States.[126]

B. *The FDA's Historical Response to the Drug Lag*

The faster availability of drugs abroad has led to calls for the FDA to adopt European and Japanese practices. The FDA's adoption of European and Japanese practices would expedite the review process[127] and encourage the FDA's entry into cooperative agreements with foreign

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extended for drugs discovered by foreign pharmaceutical firms. *Id.*

121. *See* Drug Fact Sheet, *supra* note 4, at 9. A study conducted between 1977 and 1987 revealed that the United States lags behind Great Britain in the approval of new drugs in various therapeutic categories—Respiratory: 5.1 years; Cardiovascular: 3.2 years; Central nervous system: 3.2 years; Anti-cancer: 2.9 years; Anesthetic and analgesic: 2.0 years; Gastrointestinal: 2.0 years; Endocrine: 1.4 years; Anti-infective: 0.8 years. *Id.*

122. COUNCIL ON COMPETITIVENESS, FACT SHEET 3 (1991).

123. Drug Fact Sheet, *supra* note 4, at 8; FORBES, *supra* note 3, at 25.

124. Drug Fact Sheet, *supra* note 4, at 8.

125. *See* Josef C. Brada, *Government Policy and the Transfer of Pharmaceutical Technology Among Developed Countries, in* THE INTERNATIONAL SUPPLY OF MEDICINES: IMPLICATIONS OF U.S. REGULATORY REFORM, *supra* note 33, at 37, 42-47.

126. *Id.* at 43, 45.

127. Drug Fact Sheet, *supra* note 4, at 9. For example, Great Britain does not require governmental approval prior to initiation of Phase I research. Rather, INDs are submitted to institutional review boards which can generally act on them quickly. As another example, France and Great Britain rely on outside experts to review data on behalf of the drug regulatory agencies. These outside experts minimize the problem of backlog in considering NDAs. *Id.*

drug regulatory agencies for testing new drugs.[128]

Historically, the FDA has not accepted data from foreign clinical trials as evidence of a new drug's safety or efficacy.[129] The FDA has cited its inability to monitor data collected by foreign investigations in the same manner that it can monitor tests conducted in the United States.[130] The agency has required drugs developed and tested abroad to undergo substantially duplicative testing in the United States before approving them for marketing in the United States.[131] According to one commentator, "this policy seems to have had a significant effect in delaying the introduction of foreign-discovered drugs into the United States—even those foreign drugs that represent significant advances."[132]

During the 1980s, the FDA retreated somewhat from its policy against accepting foreign clinical data. Pursuant to a regulation promulgated in 1985, the FDA promised to allow inclusion of certain "approved studies" of international research in data it considered in the approval process.[133] The case-by-case approval process required for acceptance of foreign data, however, has made this a reform of dubious value. During the 1980s, the FDA also adopted a policy of "on-going information sharing" with its counterparts in other states.[134] Under this policy, the FDA and its regulatory counterparts abroad share information submitted by drug companies concerning the effects of drugs already approved in "information sharing" states.[135] Because this policy affects only the FDA's post-marketing surveillance phase (Phase IV) of the drug approval process, however, it has no direct impact on the speed with which new drugs are approved.

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128. *See* Kramer, *supra* note 8, at F1.

129. *See* Grabowski, *supra* note 33, at 8.

130. *See id.*

131. *See id.*

132. *Id.*

133. This regulation is codified currently at 21 C.F.R. § 312.120 (1992); *see also* 21 C.F.R. § 314.106 (1992).

These regulations permitted the United States and Canada to undertake a joint review of the application for DDI, an AIDS inhibiting drug. The FDA and its Canadian counterpart announced approval of DDI on the same day. *See Drug Review Reform Announced*, PR NEWSWIRE, Nov. 13, 1991, *available in* LEXIS, Nexis Library (discussing FDA Commissioner Kessler's reaction to the joint effort).

134. *FDA Monitors*, *supra* note 74, at 28.

135. *Id.*

C. *Harmonization: A New Era of Drug Approval*

The common goal of drug regulatory agencies is to allow safe and effective drugs to reach the market. Despite this common purpose, drug regulators historically have acted in isolation in developing standards for testing drug safety and efficacy.[136] Drug testing standards and the data generated by drug tests have differed significantly across national boundaries. Consequently, new drugs poised for marketing in multiple states have been subject to multiple tests. The time and cost associated with this multiple testing have been staggering.[137]

In November 1991, as part of a comprehensive reform package, United States Secretary of Health and Human Services Sullivan announced the FDA's intent to "harmonize" the testing standards used in the United States with those used in other industrialized nations.[138] Sec-

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136. *See* Edmund W. Kitch, *The Political Economy of Innovation in Drugs and Drug Regulation Reform, in* THE INTERNATIONAL SUPPLY OF MEDICINES: IMPLICATIONS OF U.S. REGULATORY REFORM, *supra* note 33, at 71, 84-85.

137. *See International Conference Yields Results for Pharmaceutical Regulators, Industry*, Daily Rep. For Executives (BNA) No. 219, at A3 (Nov. 13, 1991) [hereinafter *International Conference*] (discussing the reduction in time and costs in drug approval under harmonization).

138. *See* Warren L. Leary, *F.D.A. is Planning to Speed Process of Approving Drugs*, N.Y. TIMES, Nov. 14, 1991, at B14.

The harmonization initiative is one of 11 major reforms of the FDA's drug approval process. Vice President Quayle, who announced the reforms, said that "[t]hese reforms will cut years off the review process. They will have the potential to save millions of lives and billions of dollars." Vice President Quayle, Remarks at the Announcement of Reforms in the FDA's Drug Approval Process (Nov. 13, 1991) (transcript on file with author).

The other reforms are:

1. External review—FDA will contract with qualified external review organizations to conduct clinical reviews of new drugs during the NDA process;
2. Expanded use of advisory committees;
3. Expanded role for institutional review boards;
4. Flexible interpretation of the efficacy standard;
5. Accelerated approval for drugs used to treat very serious, or debilitating conditions—Many of the Phase III requirements will be waived;
6. Enhanced computerization of new drug reviews;
7. A streamlined classification system for application priorities;
8. Strengthened internal systems of accountability;
9. Reduced liability costs by exempting drug manufacturers from punitive damages when a new drug has FDA approval; and
10. Greater staff and financial resources.

See Drug Fact Sheet, *supra* note 4, at 2-8.

These reforms are expected to reduce by 4.25 years (to 5.5 years) the average development and approval time for new therapies eligible for "accelerated approval," i.e., thera-

retary Sullivan hailed harmonization as the "development of common procedures [which] would reduce . . . duplication [of tests] and speed the approval of drugs worldwide."[139]

The FDA took a step toward achieving harmonization by participating in the International Conference on Harmonization (ICH) in November 1991. ICH participants included officials from drug regulatory agencies and pharmaceutical companies in the European Community (EC), the United States, and Japan.[140] These three markets account for seventy-five percent of the world's production of pharmaceutical products and ninety percent of the world's pharmaceutical research and development activities.[141] The ICH represents an attempt to develop a coordinated, cohesive body of drug testing standards that would apply to the drug regulatory systems in the EC, United States, and Japan. Outlined below are the major accomplishments of the ICH.

1. Technical Achievements

Participants in ICH "technical workshops" attempted to streamline the type of data pharmaceutical companies must report in seeking approval for new drugs.[142] Participants attempted to isolate three areas in which testing standards are different; they determined that testing stan-

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pies used to treat serious diseases or therapies for which there is no alternative therapy. The reforms will reduce by 2.75 years (to 7 years) the average development time for all other therapies. *Id.* at 1.

The cost savings are expected to be significant. A Tufts University study cited by the FDA showed that a 1.5 year reduction in FDA approval time would save $28.5 million of the $231 million average needed to market a new drug. With accelerated approval drugs, estimated total savings would be $60 million. *Id.* at 8.

139. *See* Leary, *supra* note 138, at A11.

140. *International Conference*, *supra* note 137, at A3. ICH was organized by the following drug regulatory bodies: The Commission of the European Community (CEC), Japan's Ministry of Health and Welfare, and the FDA. The conference also was sponsored by organizations representing the pharmaceutical industry: International Federation of Pharmaceutical Manufacturers Association (IFPMA), the European Federation of Pharmaceutical Industry Associations (EFPIA), the United States Pharmaceutical Manufacturers Association (PMA), and the Japanese Manufacturers Association (JPMA). *Id.*

Observers at the conference included Australia, Canada, South Africa, Sweden, Russia and the World Health Organization. *Global Harmonization on Pharmaceutical Regulations a Step Nearer*, PHARMACEUTICAL BUS. NEWS (London), Nov. 15, 1991 [hereinafter *Global Harmonization*].

141. *EC, U.S. and Japan Sign Commitment to Standardize Pharmaceutical Tests*, INT'L TRADE DAILY (BNA) (Nov. 22, 1991) [hereinafter *EC, U.S. and Japan*].

142. *See International Conference*, *supra* note 137, at A3.

dards often revolve around drug regulators' goals of quality, safety, and efficacy. At the conclusion of the ICH, officials determined that the negotiated agreements represented a significant advancement toward reducing the cost of drug approval by up to fifty percent in the states participating in the ICH.[143]

a. Minimum Data Blueprint

ICH participants adopted a "minimum data blueprint" defining data collection conditions acceptable in the EC, United States, and Japan.[144] Before the ICH, the EC, United States, and Japan had no common control conditions for conducting laboratory tests. Participants in the ICH agreed on laboratory control conditions such as humidity and temperature.[145] Control conditions now are quantified precisely; for example, test results based on data collected under "room temperature" conditions are now unacceptable because the term "room temperature" connotes different temperatures in different parts of the world.[146]

The "minimum data blueprint" will allow a drug sponsor to file the same data package in each state in which approval for a new drug is sought.[147] While regulators in each state may still evaluate the data in the manner and to the extent they desire, the drug sponsor will recognize significant savings by avoiding substantially repetitive tests in each state in which the sponsor seeks to market the new drug.[148]

b. Stability Testing

Participants in the ICH Quality Workshop examined perceived inconsistencies between the quality assurance regulations used in the three markets and considered alternatives for resolving the differences.[149] From the workshop emerged a set of harmonized procedures for determining the shelf-life of new drugs.[150] The procedures, known as "stability testing," could result in cost savings during both the development stage of a new drug and the stage at which sponsors conduct a reexamination of

143. *EC, U.S. and Japan*, *supra* note 141.

144. *Global Harmonization*, *supra* note 140; *see* Bruce Ingersoll, *Drug Approvals to Be Hastened Under New Pact*, WALL ST. J., Nov. 13, 1991, at A3.

145. *Global Harmonization*, *supra* note 140.

146. *Id.*

147. Until harmonization is complete and all inconsistent testing standards are eliminated, some duplicative testing will continue. *See id.*

148. *Id.*

149. *International Conference*, *supra* note 137, at A3.

150. *See* Ingersoll, *supra* note 144, at A3.

the new drug during its lifetime.[151]

c. Reproductive Toxicology Studies

Before the conference, the EC, the United States, and Japan each utilized different testing procedures to determine whether a new drug caused birth defects or affected fertility. The tests, known as "reproductive toxicology studies," will be harmonized after all three agree on which tests will be used in the analysis.[152] In the interim, each of the three regulatory agencies will accept data on new drugs' effects on fertility and fetal development from their international counterparts.[153]

d. LD 50 and Other Animal Testing

Officials at the ICH reached agreement in two areas of animal testing. First, they agreed to discontinue the LD 50 test, a test the agencies used to determine the lethal dose of a new drug. In the LD 50 test, investigators administered a drug at increasing levels until they reached a dosage that killed fifty percent of the laboratory animals in the study.[154] Second, they agreed to stop requiring twelve-month toxicity studies involving rodents and canines.[155] The studies now will last six months.[156] These agreements are expected to save the lives of thousands of animals and millions of dollars per year.[157]

2. Political Achievements

The fact that regulatory agencies and pharmaceutical companies from multiple states were willing to meet openly and discuss the harmonization objective may be of more significance than the specific agreements reached at the ICH.[158] The overriding accomplishment of the conference was that all three regulatory agencies were willing to commit publicly to

151. *International Conference, supra* note 137, at A3.

152. *Global Harmonization, supra* note 140; *see also EC, U.S. and Japan, supra* note 141.

153. *Global Harmonization, supra* note 140.

154. Ingersoll, *supra* note 144, at B4. This test was halted in the United States and EC a number of years ago; only Japan still required it. *Id.*

155. *Id.*

156. *Id.* Certain toxicity studies on canines still last one year. *Id.*

157. *Global Harmonization, supra* note 140.

158. *Id.* "[T]o put all the emphasis on this conference as a scientific meeting would be to distort its impact, representing as it did the first time regulators and industry have met on such a large and public stage." *Id.*

harmonization principles.[159] The conference reflected the regulators' acknowledgment that "they were all wasting a lot of money by requiring duplicate testing without contributing anything to improving health protection."[160] The FDA's presence at the ICH was particularly significant because as recently as the mid-1980s, the agency openly regarded foreign clinical data as a source too precarious on which to base a marketing approval decision.[161]

Another indication of the participants' cooperative spirit was their agreement to a "de facto moratorium" on introducing new clinical testing standards.[162] The participants regarded new, potentially inconsistent, tests as contrary to the harmonization cause.

Despite the general agreement at the conference on the merits of harmonization, some harmonization supporters feared that cultural differences, reflected in various methods of medical practice, could impede further negotiations on streamlining clinical tests.[163] Some participants also expressed their concern that the FDA's historically isolationist tendencies could result in the FDA becoming an "institutional obstacle" to harmonization.[164] This concern was fueled by the FDA's announcement that the agency could take more than eighteen months to incorporate into its own regulations the testing standards adopted at the conference.[165]

3. Future Prospects for Harmonization

The ICH participants scheduled biannual meetings in anticipation of further harmonization of clinical testing standards.[166] The ultimate goal of conference participants is a comprehensive set of harmonized standards; to achieve this objective, regular exchanges of ideas will be necessary. Participants in the ICH hope that regular meetings will make the "ICH process" more visible and will encourage participation by industrialized nations outside the EC, the United States, and Japan.[167]

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159. *See* Abrahams, *supra* note 90, § I, at 19.

160. *EC, U.S. and Japan*, *supra* note 141.

161. *See* Grabowski, *supra* note 33, at 8 (discussing United States policy toward foreign clinical trials).

162. Abrahams, *supra* note 90, § I, at 19.

163. *Id.* ("[P]rogress on testing the effectiveness of drugs has been held up by cultural differences in medical practices between regions.").

164. *Id.*

165. *See id.*

166. *Global Harmonization*, *supra* note 140.

167. *Id.*

D. *The Future: Beyond Harmonization—International Reciprocity in Drug Approval*

While harmonization is a new concept, plans already are under consideration to further internationalize the drug review process. The focus of reforms is on reciprocity, a process by which new drugs approved in select foreign countries would receive automatic approval in the United States without FDA involvement at the NDA stage.[168] The FDA now is placing a high priority on initiating bilateral discussions to establish reciprocity for approvals.[169]

The Bush Administration has explained its reciprocity plan as follows: "Two or three key countries that FDA believes have approval processes that ensure safety and efficacy standards will be selected to initiate this process. Reciprocity will be negotiated on a country-by-country basis, resulting in mutual recognition between the U.S. and certain countries of each other's drug approvals."[170]

IV. The Impact of International Regulatory Cooperation

With the ICH agreement, the FDA has promised to accept data collected in foreign clinical tests. The FDA also has committed to work with its foreign counterparts in setting common standards for testing the safety and efficacy of new drugs.[171] The FDA's announcement that it could take up to eighteen months to incorporate these basic tenets of harmonization into its own regulations,[172] however, raises concerns about the FDA's good faith in harmonizing its approval process with the approval processes of other agencies.[173]

Perhaps more important than the potential changes in the regulatory structure itself is the practical effect that harmonization will have on the speed and quality of the drug review process. For example, will harmo-

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168. Drug Fact Sheet, *supra* note 4, at 6. "Reciprocity will open markets worldwide and provide consumers with earlier access to safe and effective drugs. Reciprocity would reduce significantly the time and expense required to obtain FDA approval of a foreign-approved drug and would conserve the resources of government and industry by eliminating the need to perform duplicative reviews." *Id.*

169. *Id.*

170. *Id.* The White House acknowledges that FDA delegation of drug review to foreign governments at the NDA stage may require Congressional involvement through enabling legislation. *Id.*

171. *See EC, U.S. and Japan, supra* note 141. *See generally supra* notes 140-62 and accompanying text (discussing specific principles of harmonization).

172. Abrahams, *supra* note 90, § I, at 19.

173. *See supra* notes 38-85 and accompanying text (discussing the drug approval process).

nization hasten approval of drugs of therapeutic importance? Will drug companies benefit through harmonization and, if so, what benefits can others, such as consumers, expect to derive from the benefits to the drug companies? Finally, will the FDA's strict safety and efficacy standards be sacrificed by harmonization, leaving the public exposed to health risks not present under the FDA's current system of drug approval? The following section analyzes the probable effects of a harmonized system on the time needed for approval, the costs incurred in developing new drugs, and safety and efficacy standards.

A. *Approval Time*

Harmonization's most tangible impact in the United States will be on the speed with which manufacturers introduce new drugs clinically tested abroad before a sponsor submits them for FDA approval.[174] The data reported in these foreign trials will obviate the need for data collection by the drug sponsor at the IND stage in the United States.[175] Because the IND stage is the longest stage in the drug approval process,[176] harmonization presents an opportunity for significant time savings. The data collected in foreign clinical trials, however, will remain subject to FDA review at the NDA stage.[177]

A substantial share of the world's pharmaceutical production occurs outside the United States. In particular, firms located in the EC introduce two-thirds of all new pharmaceutical products placed on the international market each year.[178] The faster availability of such a significant number of new drugs in the United States market would be a boon to consumers and a step toward ending the "drug lag."[179]

With harmonization fully operational, new drugs introduced first in the United States still would be subject to the time-consuming data collection requirements of the IND process, a process that the FDA has pledged to shorten.[180] The EC and Japan, however, would accept data

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174. *See EC, U.S. and Japan*, *supra* note 141.

175. *See id.*

176. The IND process lasts an average of 5 years. *See* Drug Fact Sheet, *supra* note 4, at 2. *See generally* notes 45-65 and accompanying text (discussing the IND process).

177. FDA approval at the NDA stage is by no means a certainty. *See supra* notes 66-81 and accompanying text (describing the NDA process).

178. *EC, U.S. and Japan*, *supra* note 141.

179. *See* notes 117-23 and accompanying text (discussing evidence of a drug lag in marketing approval in the United States).

180. *See* Drug Fact Sheet, *supra* note 4, at 2. Under the FDA's proposed reforms, the IND stage would be shortened from 5 years to 3 ⅓ years for "accelerated approval" drugs and 4 ⅓ years for all other new drugs. *Id. See also supra* note 138 (identifying the

gathered at the IND stage in the United States thereby reducing product licensing time in those markets.[181]

B. *Costs Incurred in the Approval Process*

Harmonization will permit the drug sponsor to avoid repetitive tests in states which are parties to the ICH agreement.[182] A multinational drug firm's ability to file the same data package in each country in which it seeks approval for a new drug will provide savings in cost as well as in time.[183] Cost savings benefit drug sponsors, consumers, and government regulatory agencies.

1. Drug Sponsors

Before the ICH, drug companies diverted financial resources from research and development to comply with increasingly disparate and stringent testing standards and report formats.[184] With less funding available for research, the introduction of new drug therapies has declined[185] and

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reforms that are expected to expedite the approval process).

181. *See* Abrahams, *supra* note 90, § I, at 19.

182. *EC, U.S. and Japan*, *supra* note 141.

183. For an analysis of the direct relationship between approval time and costs incurred in gaining approval, see Edmund W. Kitch, *The Patent and the New Drug Application: An Evaluation of the Incentive for Private Investment in New Drug Research and Marketing*, *in* REGULATING NEW DRUGS, *supra* note 119, at 81, 82-83.
The primary goals of harmonization are reduced costs in gaining approval for new drugs and less time in the approval process. *International Conference*, *supra* note 137, at A3.

184. *See* Rosemary P. Wall, Note, *International Trends in New Drug Approval Regulation: The Impact on Pharmaceutical Innovation*, 10 RUTGERS COMPUTER & TECH. L.J. 317, 331 (1984).
In 1990, the costs of regulatory compliance accounted for more than 60% of the $30 billion spent on research and development by the pharmaceutical industry worldwide. Abrahams, *supra* note 90, § I, at 19. *See* Kenneth W. Clarkson et al., *The Economics of Pharmaceutical Information: International Compacts of U.S. Regulators Reform*, *in* THE INTERNATIONAL SUPPLY OF MEDICINES: IMPLICATIONS OF U.S. REGULATORY REFORM, *supra* note 33, at 86, 99 (discussing how regulatory initiatives have affected the cost of innovating); Kitch, *supra* note 136, at 82-83 (discussing the regulators' belief that increased regulation would not affect a highly profitable pharmaceutical industry: "[o]verlooked was the fact that the industry faced with increased costs for introducing new products would preserve its profitability simply by reducing the number of new products introduced.").

185. Francis J. Blee, *Commentary*, *in* THE INTERNATIONAL SUPPLY OF MEDICINES: IMPLICATIONS OF U.S. REGULATORY REFORM, *supra* note 33, at 126, 132; *see also* Hubert Bloch, *Toward Better Systems of Drug Regulation*, *in* REGULATING NEW DRUGS, *supra* note 119, at 243, 256 ("To stop its innovative activity would be tantamount to killing the research-based pharmaceutical industry . . .").

the pharmaceutical industry has been in the undesirable position of slow therapeutic innovation during an era of significant medical advancement.[186] This situation has discouraged many drug sponsors from introducing new drugs.[187]

Under a harmonized system, drug companies should have a renewed ability and incentive to engage in research and development activities. By reducing the time and financial resources committed to regulatory compliance, drug companies will be able to devote a greater proportion of their resources to discovering new drug therapies.

2. Consumers

Consumers also will realize the benefits of harmonization. With additional funds made available because of the decline in costs of regulatory compliance, drug companies will have resources to engage in the research and development of new medicines.[188] As the costs of the approval process decline, new pharmaceutical firms may enter the market.[189] Additional firms in the market will increase competition among firms and drug prices could fall as a result.[190]

Consumers are expected to benefit significantly from the emergence and growth of biotechnology firms.[191] Biotechnology firms tend to be relatively small and are new participants in the development and manufacture of drugs.[192] Because most of these firms do not have a significant number of approved drugs from which the firms can earn profits, they

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186. Wall, *supra* note 184, at 318. Kitch refers to this phenomenon as "the under investment problem." Kitch, *supra* note 136, at 72.

187. *Id.; see* Bloch, *supra* note 185, at 255 ("Theoretically, a constellation of economic, regulatory, and social pressures could lead to a state of affairs where it would become not only unprofitable, but even financially impossible for private manufacturers to stay in drug research. . ."); *International Conference, supra* note 137, at A3. "Resources are consumed in skilled personnel who could be better employed—skilled personnel are in incredibly short supply. Time is consumed, and as time is consumed, effective patent life is eroded. Erosion of patent term means lost revenue, and lost revenue undermines a company's ability to invest in research." Comment of John Griffin, director of the Association of British Pharmaceutical Industry.

188. *See International Conference, supra* note 137, at A3.

189. Sam Peltzman, *supra* note 119, at 207.

190. Tom A. Kreuzer, *International Drug Registration*, 43 FOOD DRUG COSM. L.J. 559, 560 (1988). The drug industry is expected to be under heavy governmental pressure to pass cost savings along to consumers. *See* Remarks at the Announcement of Reforms in the FDA's Drug Approval Process, *supra* note 138, at 3.

191. *See* Therese Poletti, *U.S. Drug Makers Applaud Proposed FDA Changes*, REUTERS, Nov. 13, 1991.

192. *Id.*

depend on the expeditious approval of the small number of new drugs that they have in the development pipeline.[193] Many of these firms have had difficulty surviving because their new drug offerings have become entangled in bureaucracy.[194] Harmonization will result in a faster, less expensive approval process which will make these firms more financially capable competitors in the pharmaceutical industry.

3. Government

a. Health Care Interests

There is widespread sentiment that maximizing national health care goals requires controlling the costs of health care coverage.[195] While reasons for the health care crisis extend well beyond the ambit of high drug prices and infrequent new drug introductions, harmonization offers a practical method of addressing one element of the United States health care crisis.

Harmonization could produce general societal benefits through innovation and lower drug prices. Lower drug prices might decrease the cost of health care nationwide. The more effective treatment of disease with innovative drug therapies has the potential to reduce hospital stays, doctor visits, and worker absenteeism.[196]

b. International Trade

Statistics show that United States drug companies can no longer remain profitable by marketing their products solely within the United States.[197] Because of the historically strict regulatory climate and the

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193. *Id.*

194. *Id.* For a general discussion of the involvement of biotechnology firms in drug development, see *Biotechnology to Pioneer Drug Discovery in the Next Century*, PHARMACEUTICAL BUS. NEWS (London), Jan. 10, 1992.

195. *See, e.g.*, Susan Dentzer, *Health-Care Gridlock*, U.S. NEWS & WORLD REP., Jan. 20, 1992, at 22.

196. *See* Kreuzer, *supra* note 190, at 560.

197. *See* Clarkson et al., *supra* note 184, at 99-100. During the 1940s and 1950s, when the United States was the undisputed world leader in pharmaceutical innovation, the costs of reforms would be borne in the United States and the benefits to accrue from them enjoyed there. It insulated its markets by regulation from potentially dangerous products that might be developed locally or imported from abroad. Thus, purely domestic analysis seemed appropriate. The shortcomings of this analysis began to gain recognition as observers noted the growing international scope of the industry and the declining role played by plants located in the United States. In 1955, about 40% of international shipments of pharmaceutical products from the 10 largest exporting states originated in the United States. During the next 12 years, the United States share dropped to less than

length of the approval process in the United States, pharmaceutical companies increasingly have performed initial clinical trials and original product introductions in foreign markets.[198] For example, a study found that, as of 1982, forty percent of all new drugs discovered in the United States were first tested and marketed abroad.[199]

The trade imbalance between the United States and foreign states is well documented.[200] The imbalance in the international flow of pharmaceuticals is consistent with this imbalance—in a recent year, fifty percent of the world's exports of pharmaceuticals originated in the EC.[201] In the absence of a harmonized system of drug approval, future statistics might weigh even more heavily in favor of the EC. Because the consumer market in the EC is larger than the consumer market in the United States and approval times generally have been faster in the EC, United States companies will have overwhelming incentives to relocate their operations overseas if harmonization fails to materialize.[202]

Under a harmonized system, drug companies will perform tests at the IND stage, and then they will have the opportunity to submit a common data package to the regulatory agency of each ICH participant.[203] Upon approval of the new drugs by foreign regulatory authorities, the drug companies will be able to export the drugs from the United States, thereby improving the United States export position and counteracting

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20%. The nine foreign nations increased their exports by 250%, compared with the United States growth of only 26%.

The United States is gradually becoming another market in which the international pharmaceutical industry conducts its business. It is no longer sufficient to look only at the impact of United States policy on the aggregate operations of the domestic industry, because the viability of the industry and its operations in the United States have grown increasingly independent. Studies assessing the consequences of government policy must account for both the effect on the industry and also the effect on its operations in the affected market. *Id.*

198. *See Testing Time for Drugs*, THE ECONOMIST, Aug. 7, 1982, at 69.

199. *Id.*

200. *See, e.g.*, Amy Saltzman, *Working It Out*, U.S. NEWS & WORLD REP., Feb. 17, 1992, at 15 (discussing the purported lack of work ethic in the United States as a factor contributing to economic imbalance with Japan).

201. *EC, U.S. and Japan*, *supra* note 141.

202. The EC has about 340 million residents. Greg McCune, *EC at GATT Talks Clings to Picture-Postcard Rural Life*, REUTERS, Dec. 5, 1990.

203. *See supra* notes 144-148 and accompanying text (discussing the minimum data blueprint). Even before ICH, a drug sponsor which wanted to market a new drug in the European Community needed only to submit one data package for all of the EC countries. "The Rules Governing Medicaments in the European Community" permit the free movement of medicines within the EC. Wall, *supra* note 184, at 333.

the trade imbalance in the international supply of pharmaceuticals.[204]

C. *Safety and Efficacy of New Drugs*

The stated purposes of the ICH were to reduce the costs of drug approval worldwide and to expedite the availability of new drugs to consumers.[205] Opponents of harmonization, including consumer protection groups and congressional officials, have not seriously challenged the theory that harmonization may achieve these goals. Instead, opponents have challenged the harmonization concept on the grounds that the FDA's interaction with its foreign counterparts would sacrifice the FDA's strict standards for testing the safety and efficacy of new drugs.[206]

Critics fear the uncertainty in the review process that would result from delegating any element of the approval process to foreign entities.[207] In a letter to FDA Commissioner Kessler, three members of Congress stated that "[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."[208] This criticism focuses on the inconsistency and uncertainty resulting from various standards of review among states.[209] Critics believe that consumer interest groups and drug companies would pressure reviewers to approve new drugs in foreign markets which would create an unacceptable risk that the foreign reviewers would not objectively consider the safety of new drugs.[210]

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204. *See* Kitch, *supra* note 136, at 99. The White House has established a new Working Group to study the economic implications—including issues of international tradeoff establishing common standards for clinical trials. See Drug Fact Sheet, *supra* note 4, at 6.

205. *International Conference*, *supra* note 137, at A3.

206. *See, e.g.*, Alex Barnum, *A Plan to Speed Drug Approval: White House Wants to Cut Testing of Medicines by Nearly 4 Years*, S.F. CHRON., Nov. 14, 1991 (identifying the critics of harmonization).

207. *See* Marlene Cimons, *Three Lawmakers Seek to Delay Effort to Accelerate FDA Drug Approval*, L.A. TIMES, Nov. 14, 1991, at A23 [hereinafter *Three Lawmakers*].

208. *Id.* The members of Congress writing the letter to Kessler were Sen. Edward M. Kennedy, chairman of the Senate Labor and Human Resources Committee, Rep. John D. Dingell, chairman of the House Energy and Commerce Committee, and Rep. Henry A. Waxman, chair of the energy panel's Subcommittee on Health and the Environment. *Id.*

209. *See* Bruce Ingersoll & Hilary Stout, *Plan Set to Reform Drug Approvals: 3 Democrats Resist*, WALL ST. J., Nov. 14, 1991, at B4.

210. *Id.* The critics of the harmonization plan propose that the FDA be strengthened through increased funding. *See, e.g.*, Malcolm Gladwell, *Critics Say New FDA Procedures for Approving Drugs Would Weaken Agency*, WASH. POST., Nov. 14, 1991, at A3

These criticisms appear to misconstrue the nature of harmonization. Contrary to the cited claims of the members of Congress,[211] decisions about safety and efficacy will not be delegated to foreign governments.[212] The FDA's review of new drugs will continue under a harmonized system; only clinical tests performed at the IND stage will be performed in a foreign state.[213]

Criticism of the harmonization concept erroneously focuses upon reciprocity of approval, a practice which the FDA has appointed a working group to examine.[214] With reciprocity, the FDA would yield its power in the review of the safety and efficacy of certain drugs at the NDA stage to its foreign counterparts.[215] Under such a system, the critics' claim of uncertain standards of review would be more plausible.[216]

Several members of Congress have argued that congressional involvement in the harmonization process is necessary.[217] These members believe that the FDA is effectively abdicating its authority under the 1938 Act.[218] Some members of Congress have said that harmonization would undermine the purpose for which the FDA was created: to protect the United States public from unsafe and ineffective drugs.[219]

An analysis of the 1938 Act reveals a significant degree of FDA discretion in working toward this goal of a market free of unsafe and ineffective drugs.[220] Drug approval standards, under the 1938 Act, require only that "adequate tests" of safety be conducted and "substantial evidence" of efficacy be proven.[221] In other words, the FDA can use any less costly, less complex, and less time consuming process it desires as

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(discussing the position of former FDA Commissioner Edwards, who favors increased funding).

211. *See supra* text accompanying note 210.

212. *See supra* text accompanying notes 148 and 171 (discussing FDA's continued role in drug approval).

213. *See EC. U.S. and Japan, supra* note 141.

214. *See supra* notes 168-70 and accompanying text (discussing reciprocity).

215. *See supra* text accompanying note 168 (describing how reciprocity agreements would affect the United States drug approval process).

216. This Note focuses on the merits of harmonization, not reciprocity.

217. *See* Gladwell, *supra* note 210, at A3. The administration announced that it would not seek approval from Congress on the harmonization agreement. *Three Lawmakers, supra* note 207, at A23.

218. Barnum, *supra* note 206, at A2.

219. *See* Gladwell, *supra* note 211, at A3.

220. *See* Peltzman, *supra* note 119, at 288 (discussing the generality of the 1938 Act); *see generally supra* notes 38-85 and accompanying text (discussing the drug approval process and the broad statutory parameters within which the FDA operates).

221. 21 U.S.C. § 355(d)(l), (d)(5) (1988).

long as it obtains the requisite evidence.[222] If the FDA determines that foreign data meets this standard, the agency is not statutorily barred from accepting such data. Several factors support the FDA's reliance on such foreign data.

The first factor relates to the general congruity of purpose among drug regulatory agencies throughout the world: the protection of their citizenry from unsafe and ineffective drugs.[223] With this common goal, it is unlikely that foreign drug regulators would be any more likely than the FDA to permit data in clinical trials to be fabricated or manipulated or otherwise to allow unsafe or ineffective drugs onto the market.[224]

The second factor relates to the effect of harmonization on the nature of clinical tests performed and the data reported. With a multinational consensus on the tests to be performed and the data to be reported, harmonization represents an "international system of drug regulation which would incorporate the best features of all existing national schemes."[225] In other words, harmonization of clinical testing procedures and data requirements will lead to drug regulation based on the "highest common denominator" of safety and efficacy standards.[226]

The third factor supporting reliance on foreign data concerns incentives of drug companies performing the clinical tests. Under contemporary drug approval processes, drug companies are likely to employ strict monitoring procedures and well-controlled study designs.[227] Under a harmonized system, each national drug agency will continue to review the data with the same vigor employed before harmonization.[228] Therefore, drug companies will have no more incentive to manipulate data than they did before harmonization. In fact, they may perform clinical

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222. *Synopsis of Discussions, in* REGULATING NEWS DRUGS, *supra* note 119, at 275, 288.

223. Abrahams, *supra* note 90, § I, at 19.

224. *Id.* "All regulatory authorities have the same object—to ensure people's safety. But they're going about it in different ways." (comments of Dr. William Currie, executive director of clinical and regulatory development at Merck, a major pharmaceutical manufacturer). *Id.*

225. Bloch, *supra* note 185, at 265.

226. von Grebmer, *supra* note 114, at 60-61. *See* Wall, *supra* note 184, at 339-40 (Harmonization "is unlikely to result in relaxation . . . . In order to obtain adherence by the highly developed, highly regulated nations, i.e. United States . . . and Japan, an international [agreement] on . . . drug approval standards [is] likely to tend toward more stringent rather than more lenient requirements.").

227. *See* R. Temple, *Future Perspectives of Regulations in the United States, in* INTERNATIONAL MEDICINES REGULATIONS: A FORWARD LOOK TO 1992, at 185, 190-91 (Stuart R. Walker & John P. Griffin eds., 1989).

228. *See supra* text accompanying notes 146 & 171.

tests more conscientiously based on their knowledge that they will need to perform only one round of clinical tests, data from which will be submitted to all ICH countries.[229]

Under a harmonized system, the discovery of a drug company's failure to adhere to harmonized testing standards would have international repercussions. Drug companies operate in a highly sensitive industry in which good reputations are critical to financial success and, ultimately, to survival.[230] It is unlikely that drug companies would jeopardize their worldwide reputations by reporting false or misleading clinical test results.[231]

These factors suggest that data collected outside the United States will not have the degree of mystery and uncertainty that many critics of harmonization assert. Even if some uncertainty could result from the FDA's acceptance of foreign data, this risk must be balanced against the evidence that harmonization will expedite the availability of new, potentially life-saving, therapeutic drugs to individuals in many countries.[232] The International Conference on Harmonization was motivated by the widespread recognition that lengthy approval times and high costs of innovation detract from consumer safety because needed drugs are unavailable or unaffordable.[233] Prior to the conference, many regulators were fixated on the "chauvinistic belief that each country, in isolation, [knew] what [wa]s best" for the protection of its residents.[234] Harmonization reflects the regulators' recognition that these insular policies have inhibited new drug introductions and negatively impacted domestic as well as world health goals.[235]

V. CONCLUSION

Throughout the FDA's history, the agency has asserted that information elicited from foreign clinical tests is, in general, too unreliable to

229. *See* Temple, *supra* note 227, at 190-91.

230. *See* Susan Caminiti, *The Payoff From a Good Reputation*, FORTUNE, Feb. 10, 1992, at 74 (discussing the success of Merck, a large United States-based pharmaceuticals manufacturer).

231. Another disincentive to false or misleading reporting is the possibility of tort liability. *See* Dillman, *supra* note 58, at 948-49 (discussing liability considerations of drug manufacturers).

232. *See supra* notes 174-81 and accompanying text (discussing how approval time will be expedited under a harmonized system).

233. *See* Wall, *supra* note 184, at 339.

234. *Id.* at 322.

235. *Id.*

serve as a basis for marketing approval decisions.[236] It has been the FDA's position that a purely domestic system of clinical testing would be most protective of United States consumers' interest in safety and efficacy. However, this view has several flaws.

The anti-harmonization view overstates the uncertainty created by harmonization and disregards the favorable effects of harmonization. Harmonization will require foreign drug regulators to monitor data collection in the same manner as the FDA, based on harmonized standards of monitoring that the FDA has deemed acceptable. To claim that drug regulators in the EC or Japan will be more likely than the FDA to permit data manipulation or to carry out their monitoring function in a lackadaisical manner only fosters a xenophobic notion that the FDA is more concerned about safety and more capable of ensuring it than its foreign counterparts.

Even if harmonization creates a marginal degree of uncertainty, critics of harmonization take a dangerously myopic view of consumer protection. To these critics, the slightest risk created by harmonization makes the approach undesirable. But the critics ignore, as the FDA has until recently, that one of the FDA's stated goals is to "[get] safe and effective drugs onto the market."[237] Harmonization is likely to expedite the process for testing and approving new drugs for use in the international market.[238]

The dual missions of the FDA are to keep unsafe and ineffective drugs off the market and to get safe and effective drugs onto the market.[239] Conceptually, these missions are at odds with each other. To be completely certain that no unsafe drugs would ever be available to consumers, the FDA would never approve any new drugs. Such an approach would, of course, frustrate the FDA's other mission to get safe and effective drugs onto the market. To argue in the name of consumer safety that the former mission should predominate over the latter mission is misguided. Not only does a slow review process forestall or preclude consumers from obtaining potentially life-saving therapies, the process discourages development of new drugs. As a result, drugs with beneficial effects may never be discovered.

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236. *See supra* notes 129-35 and accompanying text (discussing the FDA's view of foreign clinical data).

237. *See supra* notes 148 & 171 and accompanying text.

238. *See supra* notes 184-90 and accompanying text (discussing effect of harmonization on innovation).

239. *See supra* notes 174-81 and accompanying text (discussing approval time for new drugs under a harmonized system).

International regulatory harmonization is a conservative approach to promoting world health goals. While skepticism about harmonization is understandable, the expected benefits far outweigh the risks involved. For the FDA to revert to an isolationist approach to drug approval would be unjustifiable on both economic and ethical grounds.

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