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Prescription Drug Approval and Terminal Diseases: Desperate Times Require Desperate Measures

John P. Dillman

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Prescription Drug Approval and Terminal Diseases: Desperate Times Require Desperate Measures

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I. INTRODUCTION

Because some degree of risk is inherent in the use of all drugs, an individual nation's approach to prescription drug approval reflects that nation's balancing of medical risks and benefits. The United States, for example, has one of the most demanding prescription drug approval regimens in the world.¹ Its complicated approval process reflects a conservative approach to health care for an extremely safety-conscious market. American society has decided not to tolerate any more thalidomide tragedies,² even if that decision costs lives that unmarketed

1. See Teff, *Drug Approval in England and the United States*, 33 AM. J. COMP. L. 567, 581 (1985). For an analysis of American prescription drug approval requirements, see *infra* notes 13-50 and accompanying text.

2. Thalidomide, a sedative frequently prescribed to pregnant women in the 1950s and early 1960s as an antidote to morning sickness, caused deformities in thousands of babies. The

drugs could have saved.

Criticizing the Food and Drug Administration (FDA) for delayed market approval of promising drugs seems to have become fashionable, but the FDA's conservative approach has suited societal wishes and the tort liability system reasonably well.³ The conservative approach arose in response to societal demands that, above all else, medical care must be safe. When applied to drugs for the treatment of terminal diseases, however, this conservative approval process deserves the criticism it has engendered.⁴

With terminal diseases, a conservative approval policy can lead to increased production costs, uncertain effectiveness, and, ultimately, mortality.⁵ In the prevention and treatment of deadly and highly communicable diseases such as Acquired Immune Deficiency Syndrome (AIDS), delay in drug introduction simply means that lives will be lost.⁶ Because other countries approach the risk-benefit analysis of drugs less conservatively,⁷ people desperately needing treatment will seek foreign drugs. Thus, American society loses valuable monitoring and testing experience and protection for both society at large and people who lack the resources and contacts to search worldwide for cures.⁸ Finally, in the case of fatal conditions, swift approval of promising treatments offers valuable research insights with relatively small social or personal costs.⁹

In the case of AIDS, at least, the FDA has not ignored these criticisms. At several different levels, the FDA has made significant strides

thalidomide tragedy—and the idea that “safe” drugs could be so dangerous—gave rise to more restrictive prescription drug approval procedures in many countries. See Teff, *supra* note 1, at 567. Ironically, because thalidomide caused dramatic side effects in a relatively small class of patients, the true defect may have resulted from a labeling, and not a testing, failure.

3. As a safety-conscious people, Americans traditionally have demanded safety in medicines. See *id.* at 579-80.

4. This thesis is the focus of this Note. For a well-reasoned, contrary view, see Annas, *Faith (Healing), Hope and Charity at the FDA: The Politics of AIDS Drug Trials*, 34 VILL. L. REV. 771 (1989).

5. See *infra* notes 91-132 and accompanying text.

6. See *infra* notes 99-104 and accompanying text.

7. See *infra* notes 51-90 and accompanying text; see also Teff, *supra* note 1; Note, *International Trends in New Drug Approval Regulation: The Impact on Pharmaceutical Innovation*, 10 RUTGERS COMPUTER & TECH. L.J. 317 (1984) (comparing American, British, Swedish, and Third World approaches to regulation).

8. The FDA has made some strides in allowing importation of drugs approved in other countries, but still largely disallows use of drugs manufactured in the United States prior to FDA approval. See *infra* note 148 and accompanying text.

9. This argument merely suggests that if patients have terminal diseases and medical science has no proven cures, both have much to gain and little to lose by swift marketing approval of safe drugs. But see Annas, *supra* note 4 (advocating uniform drug approval procedures); see also *United States v. Rutherford*, 442 U.S. 544 (1979) (discussing reasons why Congress wanted the FDA drug approval system to apply to drugs for terminally ill patients).

in the research and development of AIDS drugs.¹⁰ Communication between research groups has improved, and the FDA has shortened treatment-introduction delays.¹¹ The FDA's response to AIDS, though, has taken precious time. If a more research-friendly drug approval process had been in place when AIDS first surfaced, valuable research could have commenced more quickly and, perhaps, saved lives.

Given the unique nature of terminal diseases, the wisdom of the FDA's conservative stance is questionable. For example, current FDA procedures take a timid approach to human trials.¹² Moreover, the FDA has not made a concerted effort to encourage drug production for the victims of terminal diseases that are less visible than AIDS.

In Part II this Note surveys the prescription drug approval processes of the United States and Great Britain. Historically, Great Britain's prescription drug approval system has differed substantially from the system in the United States. Examining the British approach offers some suggestions for modifying and refining the current American system. Part III analyzes the criticisms and limitations of the current American system in light of the experiences of the British system. Part IV addresses a number of considerations peculiar to the treatment of terminal diseases and urges that medicines for these diseases receive special handling. Finally, Part V proposes modest changes in the current drug approval approach that could offer real benefits in both patient care and societal protection.

II. A SURVEY OF PRESCRIPTION DRUG APPROVAL PROCESSES

A. *The American System*

Commentators have described the American prescription drug approval system as the most highly regulated system ever created to ensure a safe drug market.¹³ Before a sponsor may import, market, or transport a drug in interstate commerce, the FDA must approve the drug as being both safe and effective.¹⁴ While emphasizing patient

10. See *infra* notes 146-58 and accompanying text.

11. See *infra* note 146 and accompanying text.

12. In the present FDA system extensive toxicity tests and animal tests must occur before human testing is allowed. See *infra* notes 16-21 and accompanying text.

13. R. Cooper, *Remarks at Symposium for the 75th Anniversary of the 1906 Pure Food & Drugs Act and the Meat Inspection Act*, 37 FOOD DRUG COSM. L.J. 49, 59 (1982) (describing the American drug approval system as the "most detailed regulatory system for the protection of human subjects the world has ever seen"); see also Roberts & Biggers, *Regulatory Update: The FDA Speeds Up Hope for the Desperately Ill and Dying*, 27 AM. BUS. L.J. 403, 403 (1989).

14. J. NIELSEN, HANDBOOK OF FEDERAL DRUG LAW 14 (1986). Much debate has centered around the exact meaning of "safe" and "effective." In *United States v. Rutherford*, 442 U.S. 544, 554-58 (1979), the Supreme Court interpreted these terms as unitary standards, with the same meaning in all prescription-drug-related situations. For a recent administrative erosion of this hard

safety, this approach both delays and limits new treatment options.¹⁵ These delays particularly affect victims of terminal conditions.

Before the FDA grants its approval, a drug must pass a number of preclinical hurdles, including extensive animal tests, to determine whether the new drug is safe for use by human beings.¹⁶ In the case of chronic-use drugs, for example, these requirements include twelve-month chronic toxicity tests in two species.¹⁷ Although the FDA will accept foreign data, typically it also demands data collected in the United States, even in these preliminary tests.¹⁸ Not surprisingly, this practice does not encourage rapid and efficient drug approval.

If the preclinical investigations and laboratory animal studies indicate that the drug is reasonably safe for clinical trials and has potential for treating a specific disease, the manufacturer may file a Notice of Claimed Investigational Exemption for a New Drug (IND) with the FDA.¹⁹ The IND notice must contain, among other things, a description of both the drug composition and manufacturing and quality control methods, all information derived from preclinical investigations, statements about the drug's history, including all relevant hazards, an outline of the proposed phases of further investigation, a statement identifying an institutional review board with continuing reviewing authority over the investigation, and an agreement by the sponsor to report significant hazards and side effects.²⁰ Clinical studies on human beings may commence thirty days after the FDA receives the IND notice.²¹

Clinical trials in human beings generally occur in three phases. In Phase I the drug sponsor introduces the drug into a small group of healthy human volunteers for a short period of time.²² Although Phase I testing focuses primarily on drug safety, the drug sponsor also evaluates

line approach, see *infra* subpart IV(A)(2). See generally Note, *New Drug Approval: Lannett, The Drug Lag, and the NDA System*, 11 RUT.-CAM. L.J. 231 (1980).

15. For a discussion of drug delay in the American system, see *infra* notes 99-104 and accompanying text.

16. Note, *supra* note 7, at 323. "Preclinical tests" in this context simply means tests administered before the clinical patient testing begins.

17. Dunning, *Regulation, New Drug Development and the Question of Delay*, 41 FOOD DRUG COSM. L.J. 139, 139 (1986). For a discussion of the limitations of animal testing in general, see *infra* notes 113-27 and accompanying text.

18. Dunning, *supra* note 17, at 139. The United Kingdom, by contrast, accepts studies performed in other countries, provided that the studies appear legitimate. See *id.*

19. J. NIELSEN, *supra* note 14, at 14. As one step in shortening drug approval, the FDA proposed the IND rewrite. For a discussion of its adoption and ramifications, see Roberts & Biggers, *supra* note 13, at 424-25.

20. J. NIELSEN, *supra* note 14, at 14-15.

21. *Id.* at 15.

22. ABA AIDS COORDINATING COMMITTEE, AIDS: THE LEGAL ISSUES 139 (1988) [hereinafter ABA].

other factors, such as rates of metabolism, absorption, and elimination.²³ Apparently, the FDA uses this threshold testing to prevent toxic compounds from reaching large groups of people.

The drug sponsor first administers the drug to symptomatic patients in Phase II testing.²⁴ Phase II testing monitors drug safety in a larger population than Phase I testing and provides an opportunity for preliminary evaluations of efficacy.²⁵ Drug sponsors still do not include a large number of patients in these trials.²⁶ Phase II testing is a crucial part of the testing process because the results indicate whether the drug has any real promise for treating the condition in question.

Phase III testing usually is the final test for safety and effectiveness. In this phase the sponsor conducts at least two studies within a relatively large population²⁷ to assess, among other things, optimum dosage ranges, safety, and efficacy.²⁸ If the drug is designed for terminal diseases such as AIDS, the FDA generally has preferred to limit study enrollment to several hundred people even though thousands may seek to participate in these trials.²⁹

Sometimes the FDA adds a fourth phase that more accurately resembles postmarketing surveillance, not testing.³⁰ During Phase IV, the FDA can re-evaluate approval and demand either a recall or relabeling.³¹ Because the FDA devotes little time and attention to this postapproval monitoring,³² however, re-evaluation, recall, or relabeling are unlikely.

Although the IND has many functions, its primary function is alerting the FDA to the investigation so that the FDA can provide proce-

23. See *id.*; see also 21 C.F.R. § 312.21(a) (1990). This data aids in calculating the correct dosage.

24. ABA, *supra* note 22, at 139.

25. *Id.*

26. *Id.* In fact, sponsors generally limit these trials to the smallest number of participants necessary to obtain scientifically valid results. Comment, *The Right of Privacy in Choosing Medical Treatment: Should Terminally Ill Persons Have Access to Drugs Not Yet Approved by the Food and Drug Administration?*, 20 J. MARSHALL L. REV. 693, 700 (1987).

27. ABA, *supra* note 22, at 139.

28. J. NIELSEN, *supra* note 14, at 14.

29. ABA, *supra* note 22, at 139. For a proposal employing a parallel track, which allows patient access to "safe" drugs that are still undergoing testing for effectiveness, see *Fauci Urges "Parallel Track" Program: Critics Say ddi Trial Plan Isn't Working*, 4 AIDS Pol'y & L., Nov. 29, 1989, at 1. For the participants, drug trials are much more than a disinterested scientific endeavor; they can be a patient's only hope for treatment. For a more scientific and less individual perspective on drug trials, see Annas, *supra* note 4.

30. See ABA, *supra* note 22, at 141. Except in the case of special drugs for unique conditions, the FDA rarely uses this fourth phase. See *infra* notes 189-91 and accompanying text.

31. ABA, *supra* note 22, at 142.

32. See *id.* at 140. Although this proposition is true historically, increased statutory requirements for postapproval testing may cause postmarketing surveillance to become a prominent part of the approval process.

dures that assure patient protection and a high-quality investigation.³³ Thus, the FDA regards the IND more as a notice of investigation than as an endorsement of the investigation. The FDA, however, monitors the actual tests and requires testing institutions to establish review boards,³⁴ which ensure that technicians obtain proper consent and perform risk-benefit analyses for every patient.³⁵ The ultimate FDA review of INDs focuses on test design and the risk to test subjects.³⁶

For the sufferer of a fatal disease for which a drug sponsor is testing a treatment, a less traditional option exists.³⁷ Treatment IND allows physicians to prescribe an experimental drug to a patient before all clinical testing is complete.³⁸ The Treatment IND concept enabled AIDS sufferers to obtain Zidovudine (AZT) before formal FDA approval.³⁹ Although this method depends on a sympathetic and knowledgeable physician, Treatment IND circumvents many institutional obstacles to drug availability.

After the sponsor successfully completes the IND procedure and the data indicates that the drug is safe and effective for its intended purpose, the sponsor may file a New Drug Application (NDA) with the FDA.⁴⁰ The NDA contains information about test results, chemical composition, manufacturing methods, proposed labeling, safety, effectiveness, and other relevant data.⁴¹ The NDA may consist of tens of thousands of pages and include results from tests on thousands of subjects.⁴²

After completion of the NDA, the FDA initiates review and, if necessary, requests supplemental information. If the FDA deems the application to be complete, the FDA has sixty days to file the application and then one hundred eighty days to approve or disapprove it.⁴³ After

33. J. NIELSEN, *supra* note 14, at 15.

34. Note, *supra* note 7, at 323.

35. *Id.* At least five experts qualified to review the test results must compose this review board, although the board's main function is to protect patient welfare. Comment, *supra* note 26, at 700.

36. Note, *supra* note 7, at 323.

37. See ABA, *supra* note 22, at 142.

38. *Id.* A Treatment IND may be used if: (1) the drug is intended to treat a serious or immediately life threatening disease; (2) there is no comparable or satisfactory alternative drug or therapy; (3) the drug is under investigation in a clinical trial, or clinical trials have been completed; and (4) the sponsor is diligently pursuing FDA approval. 21 C.F.R. § 312.34(b) (1988).

39. See ABA, *supra* note 22, at 143.

40. J. NIELSEN, *supra* note 14, at 15.

41. *Id.* at 15-16. In this sense, the NDA resembles the IND requirements addressed earlier. See *supra* note 20 and accompanying text.

42. Note, *supra* note 7, at 323-24.

43. Peskoe, *The New Drug Approval Process—Changes and Impacts*, 41 FOOD DRUG COSM. L.J. 195, 195-96 (1986). Filing the drug application, in this case, simply means the FDA has acknowledged receipt of the application and regards it as an application to be approved or denied.

the FDA rules on the NDA, it issues an action letter: either an approval letter giving permission to market, an approvable letter indicating that the application is basically approvable, but deficient in some respect, or a nonapproval letter indicating the need for significant amendment to the application.⁴⁴ After receiving an approvable or nonapproval letter, the applicant must respond within ten days; otherwise, the FDA can consider the application withdrawn, further delaying the approval process.⁴⁵

At this point an unsuccessful applicant either can amend the application or ask for a notice of opportunity to be heard (NOOH).⁴⁶ If the sponsor amends the application, the FDA must act within forty-five days.⁴⁷ If the FDA issued a nonapproval letter, however, the FDA treats the amendment as a "major amendment" and has one hundred eighty days to review the amendment.⁴⁸ An applicant choosing not to amend also may request a NOOH.⁴⁹ The FDA has sixty days to provide the notice, although it may deny or postpone the hearing.⁵⁰ If the FDA grants a hearing, it still could find, of course, that the application is not approvable.

B. *The British System*

The British drug approval system resembles the American approach more closely than any other nation's system.⁵¹ For all the similarities, however, the British approach is reputed to be more "objective" and "expeditious" than the American system.⁵² Like the American procedure, the British system begins with animal testing.⁵³ The British system, though, requires six-month chronic toxicity studies in two species for chronic-use drugs.⁵⁴ American regulations also require testing in two

These time limits have no special significance in the particular context of this Note. That the FDA can wait six months before requesting more information from the sponsor, however, seems absurd.

44. *Id.* at 196.

45. *Id.* at 197-98. Once an application is deemed withdrawn, to continue in the process, the sponsor must resubmit the application. Then the FDA has 60 days to file and 180 days to approve or disapprove the application. *Id.* at 195-96.

46. *Id.*

47. *Id.* at 198.

48. *Id.*

49. *Id.*

50. *Id.*

51. Note, *supra* note 7, at 324. The similarities include, for example, animal testing requirements, multiple phases of testing, and extensive safety testing.

52. *Id.*; see also *infra* notes 79-86 and accompanying text. See generally Teff, *supra* note 1, at 572.

53. See Teff, *supra* note 1, at 576. For a general discussion on the limitations of animal testing, see *infra* notes 113-27 and accompanying text.

54. Dunning, *supra* note 17, at 139.

species, but for twice as long.⁵⁵ Also, while the United States typically requires domestic data, Great Britain will accept studies conducted in other countries.⁵⁶

The Medicines Act of 1968 (Medicines Act), which became operational in 1971, is the primary mechanism for prescription drug regulation in Great Britain.⁵⁷ The Medicines Act establishes compulsory licensing of drugs through a licensing authority composed of British health ministers, including the Secretary of State for Social Services, the Secretaries of State for Wales and Scotland, and the Department of Health and Social Services for Northern Ireland.⁵⁸ The Medicines Division of the Department of Health and Social Services issues Clinical Trial Certificates (CTCs), allowing drugs to be administered to human beings and, later, Product Licenses (PLs), allowing drug marketing.⁵⁹ These authorizations last for two and five years, respectively, after which time regulations require renewal.⁶⁰

The Committee on the Safety of Medicines (CSM), the organization responsible for the safety, quality, and effectiveness of new compounds, and the Committee on the Review of Medicines (CRM), the organization responsible for drugs in use as of 1975, advise the Medicines Division on drug approval issues.⁶¹ Although the Medicines Division may issue a license without consulting the CSM, it must consult the CSM before rejecting a PL.⁶² As in the American system, an unsuccessful sponsor may appeal, in this case to the Medicines Commission.⁶³

After approving the new drug for marketing, the CSM conducts postmarketing surveillance through the "yellow card" system.⁶⁴ When patients report adverse reactions to prescription drugs, their doctors complete and return postage-paid cards to the CSM.⁶⁵ This system en-

55. *See id.* These requirements persist in spite of considerable evidence that trials lasting longer than three months produce little new data. *See infra* note 127 and accompanying text.

56. Dunning, *supra* note 17, at 139. Although the FDA claims to accept foreign data, it also typically requires data collected in the United States. Therefore, as a practical matter, the British system is much more willing to rely on foreign data. *See supra* note 18 and accompanying text.

57. D. GREEN, *MEDICINES IN THE MARKETPLACE* 34 (1987).

58. *Id.*

59. *Id.* The American system, which requires that compounds be proven both "safe" and "effective" before human use, generally does not distinguish between permission to administer drugs and permission to market drugs. *See generally* J. NIELSEN, *supra* note 14, at 14.

60. *Id.*

61. *Id.* at 34-35.

62. *Id.* at 35.

63. *Id.* The Medicines Commission addresses these appeals and advises the Licensing Authority. *See id.*

64. *Id.* The "yellow card" system is analogous to the Phase IV testing in the American system described *supra* notes 30-32 and accompanying text.

65. D. GREEN, *supra* note 57, at 35. The present American system, by contrast, is not auto-

ables the CSM to identify patterns of adverse reactions and take action, such as advising the Licensing Authority to change the drug's data sheet, issuing a warning letter, or revoking the drug's license.⁶⁶

One fundamental difference between the American and British approaches is the British distinction between therapeutic and experimental drug use.⁶⁷ Although in Britain investigational and experimental drug use requires certification and licensing, therapeutic use by which physicians administer drugs to their own patients is excluded from the certification requirement.⁶⁸ Although this practice resembles the Treatment IND concept in the American scheme, the British system distinguished between experimental and therapeutic uses long before the creation of the Treatment IND exception.⁶⁹ More importantly, the FDA still demands stringent testing before drugs may be used for Treatment IND.⁷⁰ Thus, although the FDA has made significant strides in minimizing this difference, the Treatment IND concept does not match the flexibility of the British system.

The British system is also fundamentally different in its reliance on postmarketing surveillance, rather than more restrictive premarketing approval as in the American system.⁷¹ The FDA attempts to discover information relating to adverse drug reactions, effectiveness, and long-term toxicity in premarketing screening.⁷² The British system, on the other hand, relies on systematic, mandatory reporting of these aspects of a drug.⁷³ Although short-term testing may uncover most negative side effects, only long-term experience with a large, widely varied population will reveal the rare, and possibly more serious, reactions.⁷⁴

Yet another significant difference between these two systems is the use of apolitical committees to make approval decisions. Although the FDA is moving toward increased committee involvement in certain aspects of the drug approval process, the agency only relies on advisory committees occasionally.⁷⁵ In Great Britain these committees are rou-

matic and is much less organized.

66. *Id.*

67. W. WARDELL & L. LASAGNA, REGULATION AND DRUG DEVELOPMENT 151 (1975).

68. *Id.*

69. The British Medicines Act of 1968 predates the Treatment IND exception, announced in 1987, by a significant amount. *See supra* notes 37-39, 57 and accompanying text.

70. The Treatment IND regulations require that the drug, at a minimum, undergo concurrent testing in clinical trials. *See supra* note 38 and accompanying text. The British system imposes no testing requirements for therapeutic drug use. W. WARDELL & L. LASAGNA, *supra* note 67, at 151.

71. Note, *supra* note 7, at 325.

72. *See id.*

73. *Id.*

74. *Id.*

75. Dunning, *supra* note 17, at 141. A number of different reasons support further use of

tinely part of the approval process.⁷⁶ Furthermore, committee members in Great Britain function largely independent of both government and industry influence.⁷⁷ This committee independence is in sharp contrast to the FDA, which critics frequently charge is influenced by political pressures.⁷⁸

The differences between the two systems yield objectively demonstrable results. Comparative studies show that in a specific period Great Britain made similar new drugs available sooner than the United States and approved many additional exclusive drugs.⁷⁹ Eighty-two new drugs became mutually available in both countries between 1962 and 1971.⁸⁰ Fourteen appeared in both countries in the same year.⁸¹ Great Britain introduced forty-three drugs first with a mean lead time of 2.8 years.⁸² Only twenty-five first appeared in the United States with a mean lead time of 2.4 years.⁸³ When viewed in terms of "drug years," the total years of availability per drug, the statistics are even more startling: the United States had fifty-nine prior drug years, but Great Britain had one hundred twenty prior drug years of availability.⁸⁴ Furthermore, Great Britain had nearly four times as many exclusively available drugs in the same time period as the United States.⁸⁵ More importantly, the British have not suffered excessive new drug toxicity as a result of the

committees. The experience of multiple experts could assist in the approval process, and committees also limit the arbitrariness of individual decisionmakers. Because committees require a group of people to reach a consensus, however, they can tend to stifle innovation.

76. *Id.*

77. REGULATING NEW DRUGS 235 (R. Landau ed. 1973). Critics have questioned the FDA's independence from private industry for many years. As in other governmental areas, people with expertise tend to flow in and out of the FDA. This revolving door raises serious concerns about the independence of FDA employees. See D. GREEN, *supra* note 57, at 39 (noting arbitrary demands by individual examiners); see also ABA, *supra* note 22, at 145 (discussing economic pressures on clinical investigators).

78. See Note, *supra* note 7, at 324-25. See generally *supra* note 77. Even while working at the FDA, employees' actions may be so self-serving as to interfere with agency objectives. See Benac, *FDA Officials Subpoenaed in Insider Trading Probe*, *The Tennessean*, Apr. 4, 1991, at E4, col. 4 (reporting that FDA officials have been subpoenaed in conjunction with an investigation of stock trading based on confidential agency information).

79. REGULATING NEW DRUGS, *supra* note 77, at 240. The General Accounting Office of the United States found that 13 of the 14 drugs that the FDA determined to be "important" drugs between 1975 and 1978 became available in other industrialized countries between 2 months and 14 years before approval in the United States. See Roberts & Biggers, *supra* note 13, at 413.

80. W. WARDELL & L. LASAGNA, *supra* note 67, at 58-59.

81. *Id.*

82. *Id.*

83. *Id.*

84. *Id.* Besides introducing more drugs earlier, the British system apparently avoided introducing large numbers of dangerous or ineffective drugs. Roberts & Biggers, *supra* note 13, at 414. In fact, one study found only 90 of the 369 "ineffective" drugs available in the United States appeared in the British marketplace. *Id.*

85. W. WARDELL & L. LASAGNA, *supra* note 67, at 77.

greater availability.⁸⁶

For all the benefits of the British regulatory system, it also has costs. The average drug development time in Great Britain is approximately ten years.⁸⁷ Moreover, critics have made allegations of overregulation in Great Britain as well as in the United States.⁸⁸ After passage of the Medicines Act, for instance, drug development times increased between twenty and three hundred percent, with a median of seventy-five percent.⁸⁹ Even so, academics generally consider the British system to be less time consuming and less expensive than the American process.⁹⁰

III. CRITICISMS OF THE CURRENT AMERICAN SYSTEM

The procedural safeguards in the FDA approval system enhance the protection of the American public from dangerous drugs, but the safeguards have a number of serious side effects, including the increased monetary costs imposed by a sophisticated approval system.⁹¹ In an era of soaring medical insurance premiums, social program costs, and federal budget deficits, the cost and distribution of health care services have become major concerns. In addition, critics are concerned that increased developmental costs will cause corporations to develop fewer new drugs.⁹²

A. Cost

In the United States, bringing a chemical compound from initial synthesis to final marketing requires approximately thirteen years and one hundred million dollars.⁹³ At the outset, this capital-intensive process eliminates small drug companies from the new drug development field.⁹⁴ The large multinational companies also bear great expense in having to learn the intricacies of each market in which they operate in

86. REGULATING NEW DRUGS, *supra* note 77, at 240.

87. Teff, *supra* note 1, at 567 n.6.

88. *Id.* at 571.

89. D. GREEN, *supra* note 57, at 36.

90. *See supra* note 52 and sources cited therein.

91. *See infra* notes 93-98 and accompanying text.

92. *See infra* notes 105-12 and accompanying text.

93. Teff, *supra* note 1, at 567. Commentators frequently have suggested that the large cost is primarily due to American regulatory requirements. *See Note, supra* note 7, at 321.

94. Roberts & Biggers, *supra* note 13, at 405. Even a slight delay in approval can reduce greatly the net present value of a drug. In fact, a one-and-a-half-year reduction in new drug approval time can reduce the time necessary to recoup research and development expenditures by five years. *See id.* at 405-06 n.13. Because research-oriented firms, such as small biotechnological concerns, depend on an occasional superstar drug to recover research costs, delays in drug approval affect these firms disproportionately. *See id.*

order to reap the benefits of their new drug production.⁹⁵

Indeed, commentators and drug sponsors generally blame this astronomical cost on the American regulatory requirements.⁹⁶ To meet these stringent requirements corporations use money allocated for research and development to subsidize regulatory compliance efforts.⁹⁷ Furthermore, compliance takes time, which in turn costs money; a one-year delay in marketing can amount to as much as a ten million dollar loss because of increased regulatory costs and lost sales.⁹⁸

B. Delay

No one seriously disputes the fact that new drugs tend to reach the market more slowly in the United States than in other sophisticated drug-producing nations.⁹⁹ Commentators have studied this gap in new drug introduction between the United States and other developed, drug-producing nations, also known as the "drug lag."¹⁰⁰ For example, between the years 1962 and 1971, Great Britain had nearly four times as many exclusively available drugs and twice as many drug years of prior availability as the United States.¹⁰¹

Some commentators attribute this drug lag to medical "knowledge depletion," a theory which suggests that scientists largely have exploited the major medical breakthroughs of the 1950s.¹⁰² According to this view, further development will occur only when a new generation of discoveries arrives.¹⁰³ Because the drug lag is much more serious in the United States than in other similar countries, however, "knowledge depletion" must not be the only factor. Other reasons frequently offered to explain the drug lag include errors in the pharmaceutical industry's practices, lack of cooperation between the pharmaceutical industry and

95. See Note, *supra* note 7, at 331. For this reason and others, drug production has shifted away from the United States. See generally Note, *The Ethics and Economics of Unapproved New Drug Export*, 21 GEO. WASH. J. INT'L L. & ECON. 315, 334-36 (1987) [hereinafter Note, *Unapproved New Drug Export*].

96. See Note, *supra* note 7, at 321; see also *supra* note 93.

97. See generally Roberts & Biggers, *supra* note 13, at 331.

98. See Note, *supra* note 7, at 321; see also *supra* note 94.

99. See, e.g., D. GREEN, *supra* note 57, at 39 (stating that the "hidden cost of product licensing can be seen with particular clarity in America"); W. WARDELL & L. LASAGNA, *supra* note 67, at 77 (noting that "the United States has lagged considerably behind Britain" in new drug introduction); Teff, *supra* note 1, at 568 (noting criticisms of an "unnecessarily complex bureaucratic process" and an "unduly adversarial stance toward the pharmaceutical industry"); Note, *Unapproved New Drug Export*, *supra* note 95, at 334-39 (discussing extent and causes of the drug lag).

100. See Note, *supra* note 7, at 318; see also Note, *Unapproved New Drug Export*, *supra* note 95, at 334. See generally Note, *supra* note 14.

101. W. WARDELL & L. LASAGNA, *supra* note 67, at 77.

102. See Note, *supra* note 7, at 319.

103. *Id.*

the FDA, misdirected research, poor investigative data, and the FDA requirement that both efficacy and safety be proven.¹⁰⁴

C. Drug Development Discouraged

For all its benefits to domestic drug consumers, the FDA drug approval process also discourages new drug development. Indeed, one commentator has noted that the price of a thorough drug approval scheme that only allows the marketing of safe and effective drugs is reflected in extremely high research and development costs;¹⁰⁵ these costs correspondingly may diminish the potential for profit, causing development to suffer.¹⁰⁶ Americans lose both the direct benefits of drugs not developed and any unknown, hidden benefits.¹⁰⁷ Frequently, drugs produce unexpected, but eventually significant, benefits.¹⁰⁸ Without initial development, these beneficial effects obviously never would appear.

Furthermore, the stringent regulatory climate in the United States has led a number of American companies to transfer research and development operations to foreign countries.¹⁰⁹ Other companies either have established manufacturing and marketing affiliates outside the United States or have acquired foreign firms to conduct research to circumvent FDA regulations.¹¹⁰ Indeed, even if companies discover new drugs through research conducted in the United States, the companies still market approximately forty percent of these new drugs abroad first.¹¹¹ FDA requirements also have stifled new drug introductions abroad. Because the FDA has protected consumers so effectively, other

104. *Id.* Not surprisingly, all of these explanations relate in some way to perceived deficiencies in the American prescription drug approval system.

105. Kenney, *The Orphan Drug Act—Is It a Barrier to Innovation? Does It Create Unintended Windfalls?*, 43 *FOOD DRUG COSM. L.J.* 667, 667 (1988). One answer to this dilemma of developmental costs appears in the Orphan Drug Act, 21 U.S.C. §§ 360aa-ee (1988). By creating financial incentives, the Act purports to facilitate development of drugs for rare diseases. See Kenney, *supra*, at 667; see also Thomas, *Re-Assessing the Orphan Drug Act*, 23 *COLUM. J.L. & Soc. PROBS.* 413 (1990).

106. See note 105 and sources cited therein.

107. See D. GREEN, *supra* note 57, at 47.

108. *Id.* One example is the drug Zomax, originally prescribed as a general purpose analgesic and an anti-inflammatory agent. After more thorough study, the drug appeared to have significant use in prevention of coronary problems. *Id.* at 47-48. Other examples abound. Azathioprine, developed as an immunosuppressant, later found use as a treatment for rheumatoid arthritis and chronic active hepatitis. *Id.* at 48. For a more thorough treatment of the hidden benefits of drugs, see generally *id.* at 47-49.

109. *Id.* at 39; see also *supra* note 95 and accompanying text.

110. See Note, *supra* note 7, at 321-22.

111. *Id.* at 321. In the early 1960s American drug companies spent approximately 7% of their research expenditures overseas and made approximately 20% of total sales abroad. Note, *Unapproved New Drug Export*, *supra* note 95, at 334-35. A 1984 Department of Commerce report placed overseas research expenditures at 22% and foreign sales at 50% of the American total. *Id.* at 335.

countries regard FDA regulation as a benchmark and have emulated the FDA scheme by enacting stricter premarketing approval standards for new drugs.¹¹²

D. Questionable Efficacy of Animal Testing

One criticism frequently leveled at sophisticated prescription drug approval schemes in general, and the American system in particular, is that drug approval relies too heavily on the limited tool of animal studies.¹¹³ Both the American and the British systems require extensive animal tests before approving human use. Some tests, such as drug metabolism tests in animals, may provide useful data,¹¹⁴ but because different species metabolize substances in different ways, animal tests yield questionable data about the effects on human beings.¹¹⁵ In investigating the effect of drugs on higher functions, such as the central nervous system, animal-disease models provide particularly weak results.¹¹⁶ Also, animal models are almost useless in predicting adverse reactions with other medications used by human beings.¹¹⁷

Indeed, animal studies often fail to reveal all the potentially significant toxic effects of a drug in human beings.¹¹⁸ Some drugs that have potent side effects in human test subjects pose no problems in laboratory animals.¹¹⁹ One study of six chemically dissimilar drugs that had been tested extensively in dogs, rats, and men showed that animal testing failed to reveal more than fifty percent of the toxic effects in human beings.¹²⁰ Study results also show that at least twenty percent of the positive predictions for toxicity were false.¹²¹

Thus, animal tests can be not only underinclusive but also overinclusive. For instance, a number of drugs used successfully to treat human beings cause tumors or leukemias in animals.¹²² In fact, Sir Alexander Fleming claimed that the penicillin project was successful because he never tested the drug in animals.¹²³ Had he known of

112. Note, *supra* note 7, at 322. Great Britain, Canada, West Germany, France, Sweden, and Japan are among the nations developing drug approval systems rivaling the FDA procedures in stringency. *Id.*

113. See generally REGULATING NEW DRUGS, *supra* note 77, at 40-46.

114. D. GREEN, *supra* note 57, at 41.

115. *Id.*

116. REGULATING NEW DRUGS, *supra* note 77, at 40.

117. *Id.* at 46.

118. D. JAYASURIYA, REGULATION OF PHARMACEUTICALS IN DEVELOPING COUNTRIES: LEGAL ISSUES AND APPROACHES 111 (1985).

119. REGULATING NEW DRUGS, *supra* note 77, at 40.

120. W. WARDELL & L. LASAGNA, *supra* note 67, at 138.

121. *Id.*

122. *Id.* at 63.

123. *Id.* at 138.

penicillin's animal toxicity, Fleming said that he never would have tried it on human subjects.¹²⁴ One commentator has observed that the loss of even one drug such as penicillin because of excessively stringent animal testing requirements would harm more people than all of the drug toxicity in the history of modern drug development.¹²⁵

Finally, animal testing presents another example of the FDA's overzealous approach to premarketing testing. For example, the FDA requires twelve-month studies of repeated-dose toxicity tests in animals.¹²⁶ Members of the European scientific community generally agree, however, that these tests produce "few manifestations of toxicity after three months and no significant findings after six months."¹²⁷

E. Improper Weighing of Risks and Benefits

Some degree of risk is inherent in the use of all drugs. Although the FDA's conservative balancing has provided a number of benefits, it also has had a large societal cost. Some critics suggest that by adopting a more conservative approach to drug approval than did Great Britain, the United States lost more than it gained.¹²⁸ If today's strict FDA approval process had been in effect earlier, some argue that the agency would not have approved valuable drugs such as quinine, digitalis, fluroxine, and even aspirin.¹²⁹

The current approval process can withhold drugs of undeniable value from the marketplace. One estimate suggests that by eliminating all drug-attendant risks, the average life expectancy of Americans would increase by thirty-seven minutes.¹³⁰ Removal of all therapeutically effective medicines, on the other hand, theoretically would decrease American life expectancy by ten to twenty years.¹³¹ Even the delay of effective medicines has extreme costs. If overly restrictive drug approval processes had delayed streptomycin, para-amino salicylic acid, and isoniazid by as little as two years, one estimate suggests that two billion dollars and thirteen thousand lives would have been lost.¹³² Although new drugs necessarily present undesirable risks, withholding drugs from the marketplace has attendant risks as well.

124. *Id.*

125. *Id.*

126. D. GREEN, *supra* note 57, at 42.

127. *Id.* With the recognition that animals have rights and the rise in power of animal rights groups, animal testing probably will face more difficult challenges.

128. *See, e.g.*, W. WARDELL & L. LASAGNA, *supra* note 67, at 105.

129. *See, e.g.*, D. GREEN, *supra* note 57, at 49.

130. *Id.* at 43.

131. *Id.*

132. *Id.* at 40. These drugs were used for the treatment of tuberculosis, among other things. *Id.*; *see also* PHYSICIANS' DESK REFERENCE 1898 (1991).

IV. CORRECTIVE MEASURES

A. *Government Responses*

1. Congressional Legislation

Congress enacted the Orphan Drug Act (Act)¹³³ in 1983 to encourage the development of drugs for unique conditions.¹³⁴ By providing strong economic incentives in the form of grants, tax credits, and a period of monopoly, the Act motivates industry to develop and produce drugs to treat rare diseases.¹³⁵ While the Act has been criticized for allegedly overcompensating pharmaceutical companies,¹³⁶ the FDA designated 239 drugs as orphan drugs in the first five years of the Act's existence.¹³⁷ This program, of course, does nothing to make approval quicker or easier, but it does provide incentives for producing new drugs. Given the worldwide decline in drug development,¹³⁸ these incentives seem warranted.

2. Food and Drug Administration Actions

a. *Permanent Reforms*

For all its overzealous adherence to procedure and administrative inefficiency, the FDA has instituted some changes to address the problems of delayed drug approval. Facing mounting criticism, the FDA published a report in 1982 outlining comprehensive proposals for streamlining NDAs.¹³⁹ Known as the NDA rewrite, the proposals encompass a streamlined application format, a procedure for updating applications still under formal agency review, provisions for substituting summaries for full-length case reports, an expedited appeals process, a more liberal approach to accepting foreign data, and more thorough reporting of postmarketing problems.¹⁴⁰ At the time of the proposals, the NDA system was fraught with problems; for example, an average appli-

133. 21 U.S.C. §§ 360aa-ee (1988).

134. Kenney, *supra* note 105, at 667. *See generally supra* note 105 and sources cited therein.

135. The Act provides incentives in the form of grants, tax credits, and marketing exclusivity. Kenney, *supra* note 105, at 667 n.4.

136. Critics charge that some drug companies have reaped enormous benefits from this program. *See* Thomas, *supra* note 105, at 431. For a business viewpoint from within the pharmaceutical industry, see O'Reilly, *The Inside Story of the AIDS Drug*, *FORTUNE*, Nov. 5, 1990, at 113. The Act has suffered from confusion in the FDA interpretation of "drug" and questions about rewards for simultaneous drug development. *See generally* Kenney, *supra* note 105; Thomas, *supra* note 105.

137. Kenney, *supra* note 105, at 667.

138. *See supra* notes 105-12 and accompanying text.

139. Teff, *supra* note 1, at 570 & n.21; *see also supra* notes 40-45 and accompanying text. *See generally* Peskoe, *supra* note 43; Note, *supra* note 14.

140. Teff, *supra* note 1, at 570 & n.21.

cation was one hundred thousand pages.¹⁴¹ Through the NDA rewrite the FDA intended to decrease NDA length by seventy percent.¹⁴²

In 1983 the FDA proposed injecting more flexibility into the IND stage of the approval process.¹⁴³ These proposals attempted to provide patients with serious conditions easier access to some investigational drugs, to encourage reporting of adverse reactions, to exempt some clinical investigations from IND requirements, and to strengthen communications between drug researchers and the FDA.¹⁴⁴ These reforms promised much, but one could question their overall effectiveness.

Some observers have noted that the IND-NDA reform started losing momentum by as early as mid-1983.¹⁴⁵ Commentators attribute this slowdown to a number of causes, including resistance to deregulation in health and safety matters, a growing and influential generic drug industry, generally diminishing enthusiasm for deregulation, and changing agency practices.¹⁴⁶ In any event, IND-NDA reform apparently has not eliminated all unreasonable drug approval delays.¹⁴⁷

The FDA also has taken several steps designed to address the problems of terminally ill patients. The FDA has created two centers for AIDS research to provide direct access to AIDS-related information, has developed a separate division to review AIDS treatments such as antiviral drug products and drugs for opportunistic infections, and has granted a top priority classification for proposed AIDS therapies to ensure that the FDA gives the highest priority to review of applications for those therapies.¹⁴⁸ The FDA also developed the Treatment IND program¹⁴⁹ to provide patients access to drugs with demonstrated effectiveness against AIDS-related diseases. In 1988 the FDA instituted a policy allowing individual patients to import drugs from abroad.¹⁵⁰ Finally, Congress has committed additional resources for staff and equipment to

141. *Id.*

142. *Id.*

143. *See id.* at 570 & n.22; *see also supra* notes 19-36 and accompanying text.

144. Teff, *supra* note 1, at 570 & n.22. The final IND rewrite allows, among other things, treatment use of investigational new drugs not yet approved by the FDA for sufferers of "serious or immediately life-threatening diseases." Roberts & Biggers, *supra* note 13, at 425.

145. Teff, *supra* note 1, at 570.

146. *Id.* at 570-71. In spite of this slowdown, in the first year of the IND rewrite the FDA approved marketing of seven experimental therapies. Thomas, *supra* note 105, at 422.

147. Teff, *supra* note 1, at 571. *See generally supra* note 43 and accompanying text.

148. Weissinger, *Where Is the AIDS Problem Leading Us? A Forecast from the Center for Drug Evaluation*, 43 FOOD DRUG COSM. L.J. 767, 767-68 (1988).

149. *See supra* notes 37-39 and accompanying text.

150. *See Note, The FDA's Mail Import Policy: A Questionable Response to the AIDS Epidemic*, 16 RUTGERS COMPUTER & TECH. L.J. 169 (1990) (expressing a preference for Treatment IND policies over mail import policies); *see also* Boffey, *Importing AIDS Drugs: Analysis of F.D.A. Policy*, N.Y. Times, July 26, 1988, at C1, col. 4; Boffey, *F.D.A. Will Allow Patients to Import AIDS Medicines*, N.Y. Times, July 25, 1988, at A15, col. 1.

review drugs for AIDS treatment.¹⁵¹ Although these changes have produced positive results,¹⁵² some observers note that the most important outcome may be the increased interaction between the FDA, industry, researchers, and academia.¹⁵³

b. Interim Measures

In 1988 the FDA once again moved to speed approval of promising anti-AIDS drugs.¹⁵⁴ Although couched in language that conceivably encompassed other serious diseases, the proposal clearly resulted from public demand for AIDS treatments.¹⁵⁵ These procedures, regarded as temporary, interim procedures, allow marketing of promising drugs without Phase III clinical trials.¹⁵⁶ The FDA claimed that deleting Phase III clinical trials would reduce the human research time for new drug approval from as long as ten years to as short as two years.¹⁵⁷

The procedures, codified as "Drugs Intended to Treat Life Threatening and Severely-Debilitating Illnesses," suggest that although the FDA will apply safety and efficacy standards to all drugs, the variety of both drugs and drug uses demands flexibility in applying standards.¹⁵⁸ Initially, one must question the FDA's basic premise that the same statutory standards should apply to all drugs, particularly drugs to treat life-threatening and severely debilitating illnesses.¹⁵⁹ In the same paragraph the FDA explained that the procedures recognize that greater risks or side effects are more tolerable from drugs to treat life-threatening or severely debilitating illnesses than from drugs used to treat less serious illnesses.¹⁶⁰ While 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.¹⁶¹

151. See Weissinger, *supra* note 148, at 768.

152. See *id.*; see also *supra* note 146.

153. See, e.g., Weissinger, *supra* note 148, at 768. See generally Norris, *FDA's AIDS Program*, 12 *Nova L.J.* 1103 (1988); Roberts & Biggers, *supra* note 13.

154. *FDA Announces Interim Regulations to Speed Marketing of Promising Drugs*, AIDS POL'Y & L., Nov. 2, 1988, at 1 [hereinafter *Interim Regulations*]; see also 21 C.F.R. § 312.80 (1990).

155. See *Interim Regulations*, *supra* note 154, at 1; see also 21 C.F.R. § 312.80.

156. *Interim Regulations*, *supra* note 154, at 1; see also 21 C.F.R. § 312.82(b).

157. *Interim Regulations*, *supra* note 154, at 1.

158. 21 C.F.R. § 312.80. The FDA modeled the new rule on the procedures developed during the approval of Zidovudine (AZT). Used to treat AIDS, AZT appeared on the market after only 14 months of human testing. See Roberts & Biggers, *supra* note 13, at 436-37; *Interim Regulations*, *supra* note 154, at 1.

159. See 21 C.F.R. § 312.80.

160. *Id.* The FDA stated: "These procedures reflect the recognition that . . . patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely-debilitating illnesses, than they would accept from products that treat less serious illnesses." *Id.*

161. But see Annas, *supra* note 4, at 789-96 (arguing that the type of condition should not alter research methods).

Although the FDA claimed that it will use "flexibility" when applying the standards, the claim is virtually meaningless because the FDA has decided to apply objective standards. The FDA also has noted that these procedures especially will apply if "no satisfactory alternative therapy exists."¹⁶² Presumably, the FDA itself will determine whether an alternative therapy is satisfactory. Although this idea has some merit, it also provides an opportunity for the FDA to neglect conditions that it deems unimportant.

The FDA has explained that the procedures factor into the serious nature of the disease when evaluating the benefits of the drug.¹⁶³ Because the agency will apply objective, black letter statutory performance and safety standards, however, even if applied flexibly, the FDA clearly cannot evaluate the benefits of the drug in light of the severity of the disease. Even if flexible application of these hard line tests were possible, using an identical test for all drugs eliminates any possibility of properly weighing risks against benefits. A risk-benefit analysis seems appropriate under these circumstances, but it should be more meaningful.

In the "scope" section of the life-threatening and severely debilitating illnesses protocol, the FDA encourages manufacturers to consult with the "FDA on the applicability of these procedures to specific products."¹⁶⁴ Because the FDA has information regarding the drug's nature and its intended use at this point, however, the FDA could conduct these evaluations automatically and initiate the transfer of appropriate drugs into this protocol. Similarly, the FDA suggested that sponsors of appropriate drugs in the preliminary stages of drug development initiate meetings with FDA officials to discuss both the proposed preclinical and clinical studies.¹⁶⁵ Why must the sponsor be required to request such a meeting if the FDA values increased development of these drugs so highly? At this point in development the FDA has enough information to know whether the drug falls within these guidelines. Therefore, automatically scheduling a meeting to resolve necessary matters before preclinical and clinical tests begin seems sensible. Moreover, the FDA stated that it will honor these requests to the extent that resources permit.¹⁶⁶ Depending on the chosen interpretation, this statement either means that the agency will conduct these meetings if at all possible, or that the agency will conduct these meetings only if it deems that re-

162. 21 C.F.R. § 312.80.

163. *Id.*

164. *Id.* § 312.81(c).

165. *Id.* § 312.82.

166. *Id.*

sources permit. If these drugs really do merit the highest priority as the FDA has stated, resources always should permit.

In spite of the procedural hurdles, however, conducting meetings early in the process to direct research and development and facilitate ultimate approval is a positive step. These meetings can lead to a more meaningful and satisfactory approval process for all parties. Additionally, the FDA has increased reliance on outside, expert, and, hopefully, independent committees.¹⁶⁷ Under these procedures, which are similar to those in the British system,¹⁶⁸ the FDA may invite participation from outside expert scientific consultants.

The first round of these meetings, "[p]reinvestigational new drug (IND) meetings,"¹⁶⁹ may occur before the submission of the initial IND.¹⁷⁰ At this meeting, the FDA and the sponsor will review proposals and reach an agreement on the design of the animal studies that are needed prior to human testing.¹⁷¹ The parties also may choose to discuss the scope and design of Phase I testing, as well as appropriate standards.¹⁷²

The procedures for drugs designed for life-threatening ailments also provide that, at the sponsor's request, the sponsor can meet with the FDA at the end of Phase I clinical testing.¹⁷³ Once again, although these Phase I meetings could help process the drug more quickly, they are not automatic or mandatory.¹⁷⁴ Significantly, meeting at the conclusion of Phase I facilitates design of appropriate Phase II trials, with an aim toward eliminating the need for Phase III testing, which has been criticized as unnecessary duplication.¹⁷⁵ This possibility is particularly important for drugs designed to treat life-threatening diseases because final testing for safety and effectiveness can be done with patients in the general population as well as with patients in clinical trials. Because, by definition, terminal patients have little to lose and much to gain, the approach seems eminently reasonable.¹⁷⁶ At the end of Phase II testing, however, the FDA requires the same rigorous procedures as for the end of Phase I meetings¹⁷⁷ and demands extensive documenta-

167. *See id.* §§ 312.82, 312.84(b) (1990).

168. *See supra* note 76 and accompanying text.

169. *Id.* § 312.82(a) (emphasis omitted).

170. *Id.*

171. *Id.*

172. *Id.*

173. *Id.* § 312.82(b).

174. *See id.*

175. *See id.*

176. At least in theory, it seems that these patients have little to lose and much to gain. *But see* *United States v. Rutherford*, 442 U.S. 544, 554-59 (1979); *Annas, supra* note 4, at 777-78.

177. 21 C.F.R. § 312.82(b). These procedures include (1) submission of background information for further testing at least one month in advance of the meeting, (2) submission of summaries

tion.¹⁷⁸ Supposedly, a truly interested FDA would work toward approval, not just more procedure.

If the Phase II tests appear promising, the FDA may ask the manufacturer to submit a treatment protocol.¹⁷⁹ The FDA must "grant" the treatment protocol; thus, the agency reserves the right to delay and, quite possibly, deny approval.¹⁸⁰ Whatever advantages this protocol mechanism may have, it entails more delay in the drug's ultimate availability for patients. The FDA, however, seems to view the treatment protocol as a stopgap measure for drug availability during the period in which the sponsor assembles the marketing application and the FDA completes review.¹⁸¹ Because the FDA intends these protocols to be a temporary measure before ultimate approval or denial, a slight delay may not be significant. With a more efficient and better organized approval process, however, treatment protocols would not be necessary. Unfortunately, the FDA has attempted to correct a problem of overregulation with more regulation.

The FDA approval procedures for drugs to treat life-threatening and severely debilitating illnesses emphasize the agency's use of a risk-benefit analysis when assessing these drugs.¹⁸² Surprisingly, the agency refuses to use this analysis for ordinary drug approval. Because all drugs involve risk, an evaluation of risks and benefits seems necessary for any meaningful drug approval. To require a risk-benefit analysis only for a special class of drugs falsely implies that no risks exist with the use of other drugs.

Furthermore, the FDA's proclamation that it will weigh the risks and benefits of these drugs suggests quantitative and qualitative problems.¹⁸³ First, assigning relative weights is highly subjective. Indeed, given the personal nature of medical treatment, only a well-informed patient can perform such weighing in a meaningful manner. Only the patient truly can decide which negative side effects are per-

of investigation completed, (3) submission of plans for other nonclinical studies, and (4) labeling proposals. *See id.* § 312.47(b)(1)(iv).

178. *Id.* § 312.82(b).

179. *Id.* § 312.83. The treatment protocol must contain (1) an explanation of the intended use of the drug; (2) an explanation of the rationale for use of the drug; (3) a description of the criteria for patient selection; (4) a description of the method of administration and dosages; and (5) a description of clinical procedures, laboratory tests, and other measures to minimize risk and monitor drug effects. *Id.* § 312.35(a)(1). Furthermore, the treatment protocol is to be supported by a brochure to be supplied to each treating physician, technical information relevant to the safety and effectiveness of the drug, and a commitment by the drug manufacturer to assure compliance with the informed consent requirements of 21 C.F.R. Part 50. *Id.* § 312.35(a)(2).

180. *See id.* § 312.83.

181. *See id.*

182. *Id.* §§ 312.80, 312.84.

183. *See id.* § 312.84(a).

missible in a given situation.¹⁸⁴ Second, the FDA may undertake a balancing test, but because the risks are minor and the gains potentially great with these particular drugs, the meaningfulness of balancing is questionable. Indeed, a discussion of risks hardly makes sense to a terminal patient. Given the nature of life-threatening illnesses, imagining a scenario in which potential risks would outweigh potential benefits is difficult. A reasonable patient who is interested in any form of treatment probably will prefer not to try a promising new drug only if faced with clearly toxic compounds.¹⁸⁵

Instead of considering only the known risks of these drugs, the FDA has indicated it also will evaluate potential risks.¹⁸⁶ While normally this practice would constitute prudent policy, when individuals only have a few months to live, potential risks should not weigh heavily in the approval calculus. If the patient will die before the drug is marketed, concerns at this stage of the approval process about possible risks at some later date are frivolous.

After deciding the ultimate issue of approval, the FDA will issue an action letter coming in one of the three forms used for other drugs.¹⁸⁷ If the FDA issues either a nonapproval letter or a letter of deficiency, the agency will suggest how to correct deficiencies and provide any advisory committee recommendations regarding the application.¹⁸⁸ This procedure is a sound step by the FDA to expedite new drug availability. Also, providing committee input to help applications become approvable illustrates the potential of committees to improve the prescription drug approval process.

The new procedures for drugs to treat life-threatening and severely debilitating illnesses, unfortunately, do not carry the same enabling attitude into the question of proper time frame. The FDA has stated that the procedures and requirements of 21 C.F.R. sections 314 and 600¹⁸⁹

184. Balancing patient rights with their implied autonomy and the desire to avoid unorthodox, and sometimes dangerous, medical treatments, has proved troublesome. In a well-reasoned and thought-provoking dissent, Chief Justice Rose Bird of the California Supreme Court argued that the constitutional right to privacy extends to a patient's choice of medical treatment. *People v. Privitera*, 23 Cal. 3d 697, 711, 591 P.2d 919, 927, 153 Cal. Rptr. 431, 439 (Bird, C.J., dissenting), cert. denied, 444 U.S. 949 (1979). Concerned that patients could be forced to have or forego treatments and that orthodoxy has inhibited, not encouraged, the development of new treatment alternatives, Chief Justice Bird supported recognizing and preserving both the patient's and the physician's rights in this context. See *id.* (Bird, C.J., dissenting).

185. See generally *United States v. Rutherford*, 442 U.S. 544 (1979).

186. See 21 C.F.R. § 312.84(a) (1990). But see *Roberts & Biggers*, *supra* note 13, at 437 (suggesting that problems exist with limiting premarketing testing).

187. See 21 C.F.R. § 312.84(c); see also *supra* note 44 and accompanying text.

188. 21 C.F.R. § 312.84(c).

189. See *id.* §§ 314, 600.

govern these exceptions from standard procedures.¹⁹⁰ In other words, the FDA applies the same reviewing time frames to all drugs, including the ones designed to treat life-threatening and severely debilitating illnesses. Despite the unique nature of these conditions, the FDA has not chosen to compress the time it allows itself to review applications.

In Phase IV testing, or postmarketing surveillance, the FDA has made some strides for these unique drugs. The FDA has indicated that it may seek the sponsor's agreement to conduct some postmarketing studies,¹⁹¹ which could increase information about drug risks and benefits, optimal use dosages, and schedules of administration.¹⁹² Researchers also could derive from these studies information about the drug's effect in other patient populations or in other stages of the disease or the effect of long-term drug usage.¹⁹³ Postmarketing studies are sensible, and, coupled with simplified initial approval, these studies should offer superior drug availability with minimum risk to the patient.

Finally, the FDA has suggested that it may conduct focused regulatory research on what it deems "critical rate-limiting aspects" of the preclinical, manufacturing, and clinical phases of drug development and evaluation.¹⁹⁴ While the FDA's meaning is not completely clear, the fact that the FDA intends to take an active stance merits note. Instead of its usual reactive position, the FDA has established a mechanism for undertaking research on its own initiative.

Thus, while the critics of the procedures for drugs intended to treat life-threatening and severely debilitating illnesses may not miss the mark entirely when they argue that current regulations could have accomplished everything in these procedures, they overstate the situation.¹⁹⁵ The FDA has made some real changes in its statutory framework, and it has moved to expedite certain parts of the approval process. To sufferers of illnesses awaiting new treatments, however, these changes may be too little, too late.

190. *Id.* § 312.84(d).

191. *See id.* § 312.85.

192. *Id.*

193. *Id.*

194. *Id.* § 312.86. These terms are not defined in the new procedures.

195. Critics of the proposal included Rep. Henry Waxman (D-Calif.), who stated, "There is almost nothing in this proposal that can't be done under current regulations." *See Interim Regulations, supra* note 154, at 2. Waxman characterized the announcement as "a politically timed announcement that raises false hopes for desperately ill people." *Id.* This Note suggests that the new regulations, although not as far-reaching as they could be, inject needed flexibility into the drug approval process.

B. Liability Considerations

Over the last few decades products liability has emerged as an increasingly serious concern for prescription drug manufacturers.¹⁹⁶ Mistakes in testing or marketing can lead a company to financial ruin. Ironically, extensive FDA testing has provided one protection for prescription drug manufacturers.¹⁹⁷ If the FDA relaxes testing requirements for prescription drugs, the balance between liability and regulation, which gives tenuous protection from liability, possibly could shift. Such a shift has serious implications because increased liability exposure could decrease drug availability and, consequently, defeat the purpose of the current reforms.

Although the concerns about potentially increased liability for drug manufacturers have serious underpinnings, they need not cripple attempts to shorten drug approval delays. For one thing, the FDA has approached the problem by eliminating testing for efficacy, not safety.¹⁹⁸ Some critics argue that providing accessibility to ineffective drugs will lead patients to forsake proven treatment alternatives; therefore, providing drugs of questionable efficacy has hazards of its own.¹⁹⁹ The FDA softened its stance on drug efficacy, however, only for drugs to treat ailments for which no satisfactory alternative treatment exists.²⁰⁰ No promising discussions about allowing all patients the option of choosing alternative treatments have occurred even though sound reasons exist for exploring this option.²⁰¹

196. For a discussion of some of the reasons for this liability and its impact on the contraceptive market, see Orenstein, *The Politics of Birth Control*, GLAMOUR, Oct. 1990, at 264. This Note will not attempt to address all of the products liability concerns unique to prescription drug manufacturing.

197. By explaining FDA requirements and manufacturer efforts to meet those requirements in minute detail, a drug manufacturer would make a plaintiff's proof of negligence much more difficult.

198. See *supra* note 29 and accompanying text. The abbreviated approval programs delete Phase III testing, not Phase I or II testing. See *supra* notes 22-26 and accompanying text.

199. See Annas, *supra* note 4, at 796-97.

200. See *supra* notes 38, 162 and accompanying text.

201. See Comment, *supra* note 26, at 714 (suggesting that the right to privacy supports the proposition that terminally ill people should have access to unapproved drugs). Chief Justice Bird of the California Supreme Court in her dissenting opinion in *People v. Privitera*, 23 Cal. 3d 697, 711, 591 P.2d 919, 927, 153 Cal. Rptr. 431, 439 (Bird, C.J., dissenting), cert. denied, 444 U.S. 949 (1979), expressed her view that a cancer patient and doctor had a constitutionally protected privacy right to decide to use Laetrile as a treatment. She wrote:

Cancer is a disease with potentially fatal consequences; this makes the choice of treatment one of the more important decisions a person may ever make, touching intimately on his or her being. For this reason, I believe the right to privacy . . . prevents the state from interfering with a person's choice of treatment on the sole grounds that the person has chosen a treatment which the state considers "ineffective."

Id. (Bird, C.J., dissenting).

Pharmaceutical products liability claims may allege defects in three different areas: manufacturing, warning, or design.²⁰² Although failure-to-warn claims traditionally have constituted the majority of prescription drug litigation, an increasing number of claims allege design defects.²⁰³ Plaintiffs are unlikely to be able to prosecute successfully design-defect actions for side effects of a drug marketed solely to treat untreatable illnesses. The law already provides that if accompanied by proper warning, unavoidably unsafe products are neither defective nor unreasonably dangerous.²⁰⁴ Unavoidably unsafe products are products with known risks whose benefits outweigh those risks.²⁰⁵ Drugs designed to treat life-threatening illnesses arguably should fall within this classification.²⁰⁶ Consequently, thorough and thoughtful labeling should provide a significant measure of protection for those who sell drugs not fully approved by the FDA.²⁰⁷ Coupled with the tort requirements of proof of causation and damages, which are frequently difficult to prove in these circumstances,²⁰⁸ liability considerations should not deter drug development significantly.

V. CONCLUSION

The United States does have one of the most sophisticated and demanding prescription drug approval systems in the world partly because of a discriminating public that places great value on human life. When Americans take prescription medications, they demand safe and

202. See Schwartz, *Products Liability Law and Pharmaceuticals: New Developments and Divergent Trends*, 43 FOOD DRUG COSM. L.J. 33, 34 (1988); see also Birnbaum, *Unmasking the Test for Design Defect: From Negligence [to Warranty] to Strict Liability to Negligence*, 33 VAND. L. REV. 593 (1980).

203. Schwartz, *supra* note 202, at 33.

204. Comment, *Drug Products Liability: Duty to Warn*, 495 U. PITT. L. REV. 283, 286 (1987); see also sources cited *infra* note 205.

205. See RESTATEMENT (SECOND) OF TORTS § 402A comment k (1977); see also Schwartz, *supra* note 202, at 36-37.

206. See generally Note, *A Question of Competence: The Judicial Role in the Regulation of Pharmaceuticals*, 103 HARV. L. REV. 773 (1990) [hereinafter Note, *A Question of Competence*]; Note, *Comment K Immunity to Strict Liability: Should All Prescription Drugs Be Protected?*, 26 HOUS. L. REV. 707 (1989) [hereinafter Note, *Comment K Immunity*]; Comment, *supra* note 204.

207. See generally Fleming, *Drug Injury Compensation Plans*, 30 AM. J. COMP. L. 297, 298-304 (1982) (outlining various statutory responses to compensation for drug injury); McKenna, *The Impact of Product Liability Law on Development of a Vaccine Against the AIDS Virus*, 55 U. CHI. L. REV. 943, 963-64 (1988) (rejecting claims that governmental assumption of liability or modification of liability standards are needed); Note, *A Question of Competence*, *supra* note 206, at 785-93 (arguing for FDA preemption of tort claims); Note, *Comment K Immunity*, *supra* note 206, at 737 (suggesting placement of tort burdens on the plaintiff to prove risks of a drug outweigh the potential benefit to society); Comment, *supra* note 204, at 299-303 (proposing that the duty to warn of potential adverse drug reactions should fall on pharmacists and pharmacies).

208. Given that the users of these drugs typically only have a few months to live and certainly will die absent treatment, the plaintiff will have difficulty proving damages and causation.

effective medications. The FDA, for the most part, does deliver these safe medicines, but it does so slowly and at great cost. For many years society has paid these prices willingly.

In the case of terminal diseases and illnesses that presently have no acceptable treatments, however, the loss outweighs gains in safety. Delay in development, testing, and approval often results in death. Desperation leads to hucksters, quacks, and black market cures. Thus, however one defines the question, the most demanding prescription drug approval regimen in the world is not the answer.

Although very similar to the American system and employing many of the same safeguards, the British system recognizes drug safety as an important goal, but not to the exclusion of drug availability.²⁰⁹ To this end, the British system provides quicker drug approval without excessive new drug toxicity.²¹⁰ The FDA seems to have noted these advantages and has increased its use of independent committees²¹¹ and recognized that it should use different procedures for experimental use and treatment use.²¹²

The FDA also has promulgated special regulations for the approval of drugs for terminal diseases.²¹³ Unfortunately, these regulations saddle excellent ideas with outmoded and burdensome procedures.²¹⁴ They do establish a good starting point, however, and as interim regulations, they certainly are an encouraging first step toward a more efficient drug approval system. These regulations include some of the highlights of the British system by recognizing the importance of postmarketing surveillance, independent committee involvement, and new drug availability. The regulations also eliminate some needless testing, thereby placing a priority on testing for safety, and not efficacy.

The prescription drug approval process could benefit from more voluntary interaction and fewer governmental requirements. Better communication between the FDA, health care providers, researchers, and pharmaceutical corporations certainly would help promising drugs reach the market sooner. Presently, regulations burden drug approval with incessant delays. Also, relaxed licensing requirements in general coupled with shorter licensing times would offer increased drug availability.

209. See *supra* notes 67-86 and accompanying text.

210. See *supra* note 86 and accompanying text.

211. See *supra* note 167 and accompanying text.

212. See generally *supra* subpart IV(A)(2).

213. See *supra* notes 154-61 and accompanying text.

214. The sincerity of the FDA drug reform efforts frequently has been questioned. See *The AIDS Hoax*, Wall St. J., Mar. 18, 1991, at A14, col. 2 (calling the FDA reform efforts a "bureaucratic hoax" and a "response to great political pressure" from a "politically astute class of patients").

The FDA's response to the peculiar problems attendant to terminal diseases has flaws. The response, however, does offer a first attempt to solve these problems and indicates the direction for future FDA reforms in drug approval generally. The FDA appears to have recognized some of the limitations of the current drug approval system. Hopefully, it will continue to address these limitations to ensure the greatest benefits to patients, medical science, and society as a whole.

*John Patrick Dillman**

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