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# Notes

## GETTING THERE FIRST WITH THE BEST: THE NEED TO SHORTEN THE PRESCRIPTION DRUG APPROVAL PROCESS

### I. INTRODUCTION

Due to unnecessary time delays, high costs and safety concerns, drug regulation in the United States is in need of reform.<sup>1</sup> The United States consistently lags behind the rest of the developed world in the approval of new, innovative, and efficient medications.<sup>2</sup> Therefore, the Food and Drug Administration (FDA) needs to implement creative and effective changes in the prescription drug approval process<sup>3</sup> in order to protect the health of the American public. Most Americans think that the FDA's stringent process for approving new prescription drugs guarantees that prescription drugs are successfully monitored.<sup>4</sup> The American public assumes that safe and innovative drugs are made available to the public as quickly<sup>5</sup> and cost effectively<sup>6</sup> as possible, while unsafe<sup>7</sup> products are kept off the market.<sup>8</sup> However, this confidence placed in the FDA is unwarranted.<sup>9</sup> In the area of new drug

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1. See *infra* notes 16-62 and accompanying text.

2. See *infra* notes 16-62 and accompanying text.

3. See *infra* notes 265-353 and accompanying text.

4. Louis Lasagna, *Congress, The FDA, and New Drug Development: Before and After 1962*, 32 *PERSP. BIOLOGY & MED.* 322, 322 (1989).

5. See *infra* notes 16-24 and accompanying text.

6. See *infra* notes 25-39 and accompanying text.

7. See *infra* notes 40-62 and accompanying text.

8. Unfortunately, there is a vast discrepancy between perception and reality, especially when opinions concern the effectiveness of the FDA. Although Americans place a great deal of trust in the agency, including the erroneous belief that the FDA itself actually tests the safety and efficacy of new drugs before they are approved for sale, the FDA falls significantly short of embodying these idealized standards for drug security. Louis Lasagna, *Congress, The FDA, and New Drug Development: Before and After 1962*, 32 *PERSP. BIOLOGY & MED.* 322, 322 (1989).

9. The drug development process in the United States has been frequently criticized for being unnecessarily time-consuming and costly. John C. Petricciani, *Disease, Drugs, and Delay: Suggested Changes for the FDA*, 38 *CLINICAL RES.*, 701, 701 (1990). This criticism has come from many directions and sources. These sources include investigative bodies, pharmacologists, doctors, and economists. GENERAL ACCOUNTING OFFICE, *FDA DRUG APPROVAL—A LENGTHY PROCESS THAT DELAYS THE AVAILABILITY OF IMPORTANT NEW DRUGS*, GAO Rep. No. HRD-80-64 (1980); WILLIAM M. WARDELL & LOUIS LASAGNA, *REGULATION AND DRUG DEVELOPMENT*

development, the FDA has proven itself incapable of encouraging innovation while simultaneously ensuring the safety of the drugs it approves.<sup>10</sup>

This Note will examine the shortcomings of the FDA's drug approval process. In Section II, the weaknesses in the American prescription drug approval process will be explored.<sup>11</sup> Section III will follow the historical development of drug approval and the rise of regulation in the United States.<sup>12</sup> The most recent attempt by the President's Council on Competitiveness to reform the drug approval process,<sup>13</sup> along with its questionable ability to affect the crisis, will be investigated in Section IV.<sup>14</sup> Finally, in Section V,<sup>15</sup> this Note will offer a unique proposal for expediting the availability of new drugs through a comprehensive post-marketing surveillance system, consisting of three steps: eliminating unnecessary animal and clinical testing, limited marketing release through approved hospital pharmacies, and mandatory reporting of drug-induced reactions and effectiveness.

## II. WEAKNESSES IN THE UNITED STATES DRUG APPROVAL PROCESS

### A. Time Delays

The drug approval process in the United States is a lengthy and time-consuming process. The time between the synthesis of a New Chemical Entity (NCE) and its final FDA approval has stretched out to a startling average of twelve years.<sup>16</sup> Despite the fact that research techniques, as well as chemical and biochemical knowledge, have seen huge advances in the last twenty-five

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(1975); Barrett Scoville, *Shifting the Burden: Restructuring the Drug Review Process*, 49 CLINICAL PHARMACOLOGY & THERAPEUTICS 229, 229 (1991); SAM PELTZMAN, REGULATION OF PHARMACEUTICAL INNOVATION 19-49 (1974).

10. The FDA's processes for approving new drugs are so cumbersome that the United States suffers a significant delay in receiving innovative medical treatment in comparison to other technically advanced nations. For example, in 1988, the average review time was fifteen months in the country of first approval for the first sixteen products approved. In contrast, these same products had an average review time of 29.7 months in the United States. And even more importantly, the extra review time in the United States has not added any discernible, extra level of safety. John C. Petriccioni, *Disease, Drugs, and Delay: Suggested Changes for the FDA*, 38 CLINICAL RES. 701 (1990).

11. See *infra* notes 16-62 and accompanying text.

12. See *infra* notes 81-154 and accompanying text.

13. Recommendations to Speed Drug Approvals Issued, [1990-91 Transfer Binder] Food Drug Cosm. L. Rep. (CCH) ¶ 42,603, at 43,617 (Nov. 18, 1991) [hereinafter Recommendations].

14. See *infra* notes 155-264 and accompanying text.

15. See *infra* notes 265-353 and accompanying text.

16. Even the FDA admits the process takes too long. Gerald Meyer, the deputy director of the Center for Drug Evaluation and Research has stated, "We do a very good job of making decisions, but we don't make them in a timely manner." Ann Gibbons, *Can David Kessler Revive the FDA?*, 252 Science 200, 201 (1991).

years, the number of NCEs introduced into the United States over this same time period has dropped by fifty percent.<sup>17</sup> This delay in the introduction of new prescription drugs in America is commonly known as a "drug lag."<sup>18</sup> That is, people living in other countries have access to useful drugs before they are available in the United States. Critics assert that the reduced innovation and competition is attributable to the excessively severe FDA regulations for new drug approval.<sup>19</sup> On the other hand, Donald Kennedy, the former Commissioner of the FDA, insists that the drug lag is an international phenomenon having little to do with the regulatory climate in the United States.<sup>20</sup> Mr. Kennedy considers the drug lag a natural result of an exhaustion of basic scientific knowledge, knowledge on which drug companies' earlier breakthroughs were based.<sup>21</sup> Mr. Kennedy states that the downward trend in drug development can only be reversed through "basic innovations in molecular biology, fresh insights in our understanding of certain disease mechanisms, or new therapeutic concepts."<sup>22</sup>

Mr. Kennedy's understanding of the drug lag ignores the fact that the United States trails other developed countries in the marketing of innovative medical treatment.<sup>23</sup> Other experts argue that the regulatory complexity of the FDA is largely responsible for the fact that fewer new drugs have been introduced in the United States in the past twenty years than in numerous other

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17. The rate of introduction of New Chemical Entities (NCEs) into the United States market has declined from over 50 in 1960 to 21 in 1989. In 1985, the FDA cleared a record number of new drug approvals by approving a total of 30 NCEs. The three year period of 1987-1989 showed a modest decrease in the rate of NCEs approved compared with the previous three year period. These data suggest that the much heralded, record number of NCE approvals in 1985 did not indicate a trend toward a greater number of annual drug approvals. Kenneth I. Kaitin et al., *The New Drug Approvals of 1987, 1988, and 1989: Trends in Drug Development*, 31 J. CLINICAL PHARMACOLOGY 116, 120 (1991).

18. William Wardell, *The Drug Lag Revisited: Comparison by Therapeutic Area of Patterns of Drugs Marketed in the United States and Great Britain from 1972 through 1976*, 24 CLINICAL PHARMACOLOGY & THERAPEUTICS 499, 499 (1978).

19. Criticism abounds from many sources. See *infra* notes 70-76 and accompanying text.

20. Donald Kennedy, *A Calm Look at "Drug Lag,"* 239 JAMA 423, 423 (1978).

21. *Id.* at 425.

22. *Id.*

23. The FDA utilizes a therapeutic rating system which classifies NCEs by their therapeutic potential. NCEs that represent important therapeutic gains are classified 1A, while those that represent modest gains are classified 1B. In a survey on the delay between foreign marketing of a new drug and the United States approval of the same drug, it was found that there was a delay of 8.9 years for 1A drugs and 9.1 years for 1B drugs. Kenneth I. Kaitin et al., *The New Drug Approvals of 1987, 1988, and 1989: Trends in Drug Development*, 31 J. CLINICAL PHARMACOLOGY 116, 121 (1991).

developed countries.<sup>24</sup>

### B. Cost

Another factor seriously limiting the innovation of new drugs in the United States is the overwhelming cost of bringing a new prescription drug to market.<sup>25</sup> A report from the Center for the Study of Drug Development at Tufts University found it takes an average of \$231 million to get one new medicine from the laboratory to the pharmacist's shelf.<sup>26</sup> Commentators and drug sponsors generally blame this astronomical cost on the American regulatory requirements.<sup>27</sup> To meet stringent FDA requirements, corporations use money allocated for research and development to pay for regulatory compliance efforts.<sup>28</sup> This means that money dedicated to the discovery and development of innovative medical treatment is instead consumed by everyday regulatory compliance.<sup>29</sup>

Furthermore, as illustrated above,<sup>30</sup> compliance takes time, which in turn raises costs. A one-year delay in marketing can result in as much as a ten million dollar loss because of increased regulatory costs and lost sales.<sup>31</sup> Because a company's patent on a medicine is valid for only a limited time, reducing the approval time means more time for exclusive sales and possibly lower prices for patients.<sup>32</sup>

The costs accruing from the lack of needed medications can be illustrated

24. William Wardell, *The Drug Lag Revisited: Comparison by Therapeutic Area of Patterns of Drugs Marketed in the United States and Great Britain from 1972 through 1976*, 24 CLINICAL PHARMACOLOGY & THERAPEUTICS 499, 521 (1978).

25. David Hanson, *Pharmaceutical Industry Optimistic About Improvements at FDA*, 70 CHEMICAL & ENGINEERING NEWS 28, 28 (1992).

26. *Id.*

27. Note, *International Trends in New Drug Approval Regulation: the Impact on Pharmaceutical Innovation*, 10 RUTGERS COMPUTER & TECH. L.J. 317, 321 (1984).

28. It is virtually undisputed that regulatory requirements have increased research and development costs, cut effective patent lives, and concentrated research and development capabilities in large pharmaceutical companies that can afford the needed budgetary outlays. Barry S. Roberts & Sara M. Biggers, *Regulatory Update: The FDA Speeds Up Hope for the Desperately Ill and Dying*, 27 AM. BUS. L.J. 403, 404 (1989).

29. *Id.*

30. See *supra* note 24 and accompanying text.

31. Even a slight delay in approval can greatly reduce the net present value of a drug. A one and a half year reduction in the approval time for a new prescription drug can reduce by five years the time it takes to recoup research costs. Barry S. Roberts & Sara M. Biggers, *Regulatory Update: The FDA Speeds Up Hope for the Desperately Ill and Dying*, 27 AM. BUS. L.J. 403, 405-06 n.13 (1989).

32. David Hanson, *Pharmaceutical Industry Optimistic About Improvements at FDA*, 70 CHEMICAL & ENGINEERING NEWS 28, 28 (1992).

through an examination of these costs saved once medication becomes available to needy patients. For example, one study showed that during the years of 1954-1969, reduction in hospitalization costs of approximately \$4 billion was made possible by the development of new anti-tuberculosis drugs.<sup>33</sup> It is estimated that \$2 billion is saved annually by using the polio vaccine.<sup>34</sup> The new measles vaccine has produced an annual savings of nearly \$180 million, as well as averting millions of cases of acute measles and thousands of cases of mental retardation each year.<sup>35</sup>

Amendments to the Food, Drug & Cosmetic Act of 1906<sup>36</sup> have resulted in progressively higher costs for bringing a new prescription drug to market.<sup>37</sup> It has been calculated that the 1962 Amendments<sup>38</sup> resulted in a net annual loss to consumers of \$250 million to \$350 million.<sup>39</sup>

### C. Safety

In addition to the lengthy delays and expensive costs associated with FDA regulation, the FDA's narrow constraints force American consumers to use less effective prescription drugs with greater toxic side effects.<sup>40</sup> Statistics concerning probability of lives lost due to the unavailability of necessary

33. MILTON SILVERMAN & PHILIP R. LEE, PILLS, PROFITS & POLITICS 14 (1974).

34. *Id.*

35. *Id.*

36. Act of June 30, 1906, ch. 3915, 34 Stat. 768.

37. Studies have shown that the 1962 Drug Amendments doubled the research and development expenditures necessary to generate a given flow of new products. Experts also contend that portions of The Drug Price Competition and Patent Term Restoration Act of 1984 create additional time delays. Barry S. Roberts & Sara M. Biggers, *Regulatory Update: The FDA Speeds Up Hope for the Desperately Ill and Dying*, 27 AM. BUS. L.J. 403, 405-10 (1989).

38. Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (codified as amended at 21 U.S.C. §§ 301-392 (1988)).

39. Due to a high number of uncertainties, economic studies attempting to show that the costs of extensive regulation outweigh the benefits are necessarily speculative. A study based on an elaborate system of consumer surplus theory analyzed the costs and benefits of the 1962 Kefauver-Harris amendments to the Food, Drug, and Cosmetic Act of 1938. By extrapolating trends in the demands for drugs before 1962, the study concluded that the reduced innovation and competition attributable to the Amendments (offset by the savings on the purchase of ineffective drugs) has resulted in a net annual loss to consumers of \$250 million to \$350 million. Although increased regulation was imposed to reduce consumer waste by eliminating ineffective or unsafe new drugs, the cost imposed on the consumer has, in reality, outweighed the benefits. SAM PELTZMAN, *REGULATION OF PHARMACEUTICAL INNOVATION 19-49* (1974).

40. Many recently developed drugs demonstrate substantially greater effectiveness in the treatment of illnesses. To the extent that the FDA delays the introduction of these new, innovative drugs, the regulatory process exposes Americans to greater health risks by forcing them to rely upon less effective medications with greater toxicity and higher incident of side effects. Barry S. Roberts & David Z. Bodenheimer, *The Drug Amendments of 1962: The Anatomy of a Regulatory Failure*, 1982 ARIZ. ST. L.J. 581, 597-98 (1982).

medications are difficult to estimate. However, the delayed introduction of safe and effective new drugs into the United States continues to cost the health and, indeed, the lives of many Americans.<sup>41</sup> Negative effects of the two major prescription drug related crises<sup>42</sup> caused approximately 100 deaths<sup>43</sup> and nine recorded instances of congenital birth defects<sup>44</sup> in the United States. These injuries and deaths resulted in a public outcry that was responsible for the passage of drug reform legislation.<sup>45</sup> Yet, these deaths were significantly less in number than the deaths that have resulted from the FDA's current system of strict enforcement of new drug regulations that delay the availability of life-saving prescription drugs.<sup>46</sup>

For example, an anti-epilepsy drug, sodium valproate, was introduced in 1967 in France,<sup>47</sup> and in 1972 in Great Britain,<sup>48</sup> but due to the drug lag in this country, the exact same drug remained unavailable for use by American patients until 1978.<sup>49</sup> The congressionally instituted National Commission for the Control of Epilepsy and Its Consequences estimated that the absence of this single drug from the United States market subjected American patients to approximately 1,000,000 unnecessary seizures per year at a cost of approximately \$200 million annually.<sup>50</sup>

Another example can be seen in the United States' delay in approving the

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41. In 1976, the President's Biomedical Panel warned that the delays and costs that the FDA's protective system impose on drug development constitute a hazard to public health. American patients have suffered a net therapeutic loss due to the conservative policies of the FDA. SCIENCE AND TECHNOLOGY POLICY OFFICE OF THE NATIONAL SCIENCE FOUNDATION, CHEMICALS AND HEALTH: REPORT ON THE PANEL ON CHEMICALS AND HEALTH OF THE PRESIDENT'S SCIENCE ADVISORY COMMITTEE 111-13 (1973); U.S. DEPT. OF HEALTH, EDUC., AND WELFARE, REPORT OF THE PRESIDENT'S BIOMEDICAL RESEARCH PANEL: APPENDIX A: THE PLACE OF BIOMEDICAL SCIENCE IN MEDICINE AND THE STATE OF THE SCIENCE 19-20 (1976).

42. The two major prescription drug tragedies resulted from the use of Elixir Sulfanilamide and the use of thalidomide. See *infra* notes 125-150 and accompanying text.

43. MILTON SILVERMAN & PHILIP R. LEE, PILLS, PROFITS, & POLITICS 86 (1974).

44. Arthur H. Hayes, *Food and Drug Regulation After 75 Years*, 246 JAMA 1223, 1224 (1981).

45. The use of Elixir Sulfanilamide led to the adoption of the Food, Drug and Cosmetic Act of 1938 and the use of thalidomide led to the 1962 Amendments of the Act. See *infra* notes 125-150 and accompanying text.

46. See *infra* notes 47-61 and accompanying text.

47. Barry S. Roberts & Sara M. Biggers, *Regulatory Update: The FDA Speeds Up Hope for the Desperately Ill and Dying*, 27 AM. BUS. L.J. 403, 404 (1989).

48. William M. Wardell, *The Drug Lag Revisited: Comparison by Therapeutic Area of Patterns of Drugs Marketed in the United States and Great Britain from 1972 through 1976*, 24 CLINICAL PHARMACOLOGY & THERAPEUTICS 499, 517-18 (1978).

49. *Id.*

50. *Id.* at 518.

drug timolol, a beta blocker used in the treatment of cardiovascular disease.<sup>51</sup> Because cardiovascular disease is the leading cause of death in the United States,<sup>52</sup> delays in the approval of drugs in this area exact a serious toll on the health of the American public. Beta blockers have been described as the most important advancement of the century for the treatment of hypertension and heart disease.<sup>53</sup> However, a significant time lag between their approval for use in European countries and approval in the United States exists.<sup>54</sup> By 1976, the availability of beta blockers in the United States was limited to a single drug; in comparison, nine were available for use in Britain at the same time.<sup>55</sup> Although timolol was already safely in use in several European countries, the FDA delayed its approval of timolol in the United States for seven years, costing an estimated 100,000 American lives.<sup>56</sup>

Yet another beta blocker, metoprolol, could have saved 100,000 hypertension patients from infarctions<sup>57</sup> and ischemic<sup>58</sup> heart diseases, had it been timely introduced in the United States.<sup>59</sup> The FDA's three year delay in approving metoprolol subjected hypertensive patients to significant physical damage due to the unavailability of the drug.<sup>60</sup> Delays in releasing other drugs caused similar losses.<sup>61</sup>

51. *Id.* at 505-06.

52. *Id.*

53. When awarding the 1976 Lasker prize for clinical research to Drs. Raymond Ahlquist and James Black, the respective discoverers of beta receptors and the clinical significance of beta blockade, the Lasker jurors described beta blockers as one of the most important classes of drugs to be discovered in this century. Beta blockers have been helpful in treating a number of different kinds of illnesses. *Id.* at 505.

54. *Id.*

55. *Id.*

56. Former Commissioner Hayes of the FDA had estimated that timolol would prevent 17,000 deaths annually from secondary myocardial infarction. Anthony Hayes, *Current FDA Directives for Promoting Public Health*, 39 AM. J. HOSP. PHARMACY 427, 428 (1982); Barry S. Roberts & David Z. Bodenheimer, *The Drug Amendments of 1962: The Anatomy of a Regulatory Failure*, 1982 ARIZ. ST. L.J. 581, 597 (1982).

57. Infarctions are defined as reoccurrence of a heart attack or an interruption of the blood supply to the heart. TABER'S CYCLOPEDIA MEDICAL DICTIONARY 721 (14th Ed. 1981).

58. Ischemic is defined as a decrease in the blood supply to a body organ or part. *Id.* at 753.

59. Barry S. Roberts & David Z. Bodenheimer, *The Drug Amendments of 1962: The Anatomy of a Regulatory Failure*, 1982 ARIZ. ST. L.J. 581, 597 (1982).

60. *Id.*

61. In the area of cancer treatment, the United States lagged behind thirty-one other countries in its approval of the anti-cancer drug anadriamysin. No reports have yet attempted to quantify the consequences of the four year delay in the United States approval of this drug. Because this drug represents the second most widely prescribed anti-cancer drug in the world, it is likely that American patients received less effective treatment than if the drug had been available. Rifampin is the favored drug for treating tuberculosis. Although 30,000 people still contract tuberculosis annually, the FDA did not approve rifampin until four years after it had become available in foreign markets. *Id.* at 598.



Historically, a relatively small amount of injury to the public's health provided cause for reform of the drug approval process. In 1937, the sulfanilomide disaster took approximately 100 lives and resulted in the passing of new drug regulations. The unfortunate incident involving the drug thalidomide resulted in nine cases of birth defects in the United States. This in turn was the driving force behind the 1962 drug reforms. Yet, the current drug approval system costs hundreds of thousands of American lives through the unavailability of necessary drugs. These lives should be considered as significant and provide the impetus for revising the drug approval process.

The FDA's slow and cautious approval of new drugs is intended to result in such benefits as decreased approval of unsafe or ineffective drugs in the United States. Instead, increased regulation of prescription drug approval has not decreased incidents of unsafe or ineffective drug approval in the United States.<sup>62</sup>

#### D. Summary

Under the stimuli of the 1962 Drug Amendments<sup>63</sup> as well as substantial appropriations<sup>64</sup> and heavy congressional oversight,<sup>65</sup> the FDA has imposed increasingly sophisticated and elaborate controls on drug research involving human subjects.<sup>66</sup> One observer has described the American drug approval process as "the most detailed regulatory system for the protection of humans the world has ever seen."<sup>67</sup> The FDA's regulatory scheme, launched by the 1962

62. SAM PELTZMAN, REGULATION OF PHARMACEUTICAL INNOVATION 48 (1974).

63. 76 Stat. 780, § 103(b) (1962) (current version at 21 U.S.C. § 355(i) (1988)) (amending § 505(i) of the Act).

64. On the origins and budgeting for the FDA's Bioresearch Monitoring Program, see, e.g., *Preclinical and Clinical Testing by the Pharmaceutical Industry, 1977: Hearings before the Subcomm. on Health and Scientific Research of the Senate Comm. on Human Resources*, 95th Cong., 1st Sess. 29-32 (1977) (S. Gardner).

65. For examples of congressional oversight, see, e.g., *Preclinical and Clinical Testing by the Pharmaceutical Industry, 1979: Hearings before the Subcomm. on Health and Scientific Research of the Senate Comm. on Labor and Human Resources*, 96th Cong., 1st Sess. (1979); *Preclinical and Clinical Testing by the Pharmaceutical Industry, 1978: Hearings before the Subcomm. on Health and Scientific Research of the Senate Comm. on Human Resources*, 95th Cong., 2d Sess. (1978); *Preclinical and Clinical Testing by the Pharmaceutical Industry, 1977: Hearings before the Subcomm. on Health and Scientific Research of the Senate Comm. on Human Resources*, 95th Cong., 1st Sess. 29-32 (1977) (S. Gardner).

66. Proposal, 43 Fed. Reg. 35,186 (1978); Protection of Human Subjects; Standards for Institutional Review Boards for Clinical Investigations, 21 C.F.R. pts. 16, 56 (1981); Proposal, 44 Fed. Reg. 47,713 (1979); Protection of Human Subjects; Informed Consent, 46 Fed. Reg. 8942 (1981) (codified in scattered parts 21 C.F.R.). In some instances research has been brought into compliance with proposed regulations, even before final regulations have been issued.

67. Harvey Teff, *Drug Approval in England and the United States*, 33 AM. J. COMP. L. 567, 581 (1985).

Amendments, had the yet unrealized goal of improving the quality and safety of drugs introduced in the United States.<sup>68</sup> However, the increased regulatory burdens have retarded the drug approval process and discouraged the innovation of new drugs.<sup>69</sup> As a result, American patients continue to suffer and die from diseases that could be successfully treated with drugs already available, and used safely, in other countries.

Criticism and suggestions for change have continuously plagued the FDA.<sup>70</sup> Legislative commissions and committees,<sup>71</sup> General Accounting Office inquiries,<sup>72</sup> executive branch studies,<sup>73</sup> congressional hearings<sup>74</sup>, and

68. S. REP. NO. 1744, 87th Cong., 2nd Sess. 8 (1962).

69. Pharmaceutical companies claim that it costs \$231 million dollars and an average of twelve years to bring a new drug to market. Ann Gibbons, *Can David Kessler Revive the FDA?*, 252 SCIENCE 200, 201 (1991). Like all businesses, the actions of pharmaceutical companies are primarily determined by economic directives. The price of hundreds of millions of dollars to research and bring to market a single drug prohibits development of new drugs that fail to bring fast and significant monetary return. Therefore, medications that would effect small portions of the world's population, or large sections of the world's poor population, would not warrant the attention of the economically minded pharmaceutical companies. One example involves the area of tropical disease research. Despite the fact that seventy five percent of the world's population is at risk of these diseases, the pharmaceutical industry refuses to take any measurable interest in developing medical treatments for tropical diseases. As one research director of a United States based drug company explains:

Of course, we could go into a big program on, say, tropical sleeping sickness or Chagas' disease. We might put in three, or four, or five million dollars a year. In five or ten years, we might hit on a useful new compound that could help a lot of people in Africa or South America. They would like to have it, but neither they nor their government could afford to pay much for it. They have the disease but not the money. My stockholders would have my scalp.

MILTON SILVERMAN ET AL., *PRESCRIPTIONS FOR DEATH: THE DRUGGING OF THE THIRD WORLD* 99 (1982). The purely economic focus of the drug industry combined with the extensive time lag of the approval of new drugs, compounds the injury to the consumers. In the period between 1972 and 1976, 2.6 times as many drugs became exclusively available in Great Britain than in the United States. The United States continues to lag behind European countries in the approval of many important drug categories, including cardiovascular drugs, peptic ulcer drugs, and central nervous system drugs - such as therapies for depression, epilepsy, and migraine. William M. Wardell, *The Drug Lag Revisited: Comparison by Therapeutic Area of Patterns of Drugs Marketed in the United States and Great Britain from 1972 through 1976*, 24 CLINICAL PHARMACOLOGY & THERAPEUTICS 499, 499 (1978). Data for new drug approvals from 1987-1989 show that eighty percent of new drugs approved in the United States were already available in foreign markets before the United States approval, with a mean of 6.5 years of prior marketing. These data are consistent with the figures for previous years and suggest little change in the rate of new drug development and review in the United States. Kenneth I. Kaitin et al., *The New Drug Approvals of 1987, 1988, and 1989: Trends in Drug Development*, 31 J. CLINICAL PHARMACOLOGY 116, 116 (1991).

70. John C. Petricciani, *Disease, Drugs, and Delay: Suggested Changes for the FDA*, 38 CLINICAL RES. 701, 701 (1990).

71. *Id.*

72. GENERAL ACCOUNTING OFFICE, *FDA DRUG APPROVAL--A LENGTHY PROCESS THAT DELAYS THE AVAILABILITY OF IMPORTANT NEW DRUGS*, GAO Rep. No. HRD-80-64 (1980).

public press commentaries<sup>75</sup> have focused on the agency and its shortcomings.<sup>76</sup> But there has been little substantive change made in the drug approval process in the last twenty-five years.<sup>77</sup> The most recent attempt to hasten the FDA's drug approval process, recommendations by the President's Council on Competitiveness<sup>78</sup> that were adopted by the FDA in 1992,<sup>79</sup> are unlikely to have any real effect on the drug lag suffered by the United States.<sup>80</sup>

### III. THE RISE OF REGULATION

The history of federal drug regulation in the United States follows a distinct pattern of little concern until a crisis erupts.<sup>81</sup> Congressional involvement remained minimal until an informed and angry public rallied at its gates.<sup>82</sup> Responses were shortsighted,<sup>83</sup> poorly conceived,<sup>84</sup> and geared toward the resolution of an immediate problem.<sup>85</sup> Reforms have enjoyed zealous short-term enforcement until the issue of drug regulation faded from public memory, at which time the governmental approach returned to the laissez-faire approach stemming from the bureaucratic mind-set still operating in the United States.<sup>86</sup>

The first recorded governmental involvement in regulating pharmaceutical

73. John C. Petricciani, *Disease, Drugs, and Delay: Suggested Changes for the FDA*, 38 CLINICAL RES. 701, 701 (1990).

74. *Reform of FDA Drug Review Process: Hearing of the Human Resource and Intergovernmental Relations Subcomm.*, Federal News Service, March 19, 1992; *Preclinical and Clinical Testing by the Pharmaceutical Industry*, 1979: *Hearings before the Subcomm. on Health and Scientific Research of the Senate Comm. on Labor and Human Resources*, 96th Cong., 1st Sess. (1979); *Preclinical and Clinical Testing by the Pharmaceutical Industry*, 1978: *Hearings before the Subcomm. on Health and Scientific Research of the Senate Comm. on Human Resources*, 95th Cong., 2d Sess. (1978);

75. John C. Petricciani, *Disease, Drugs, and Delay: Suggested Changes for the FDA*, 38 CLINICAL RES. 701, 701 (1990).

76. *Id.*

77. *Id.*

78. *Improving the Nation's Drug Approval Process*, HHS News and President's Council in Competitiveness Fact Sheet, Nov. 13, 1991.

79. See *infra* note 168 and accompanying text.

80. See *infra* notes 177-264 and accompanying text.

81. Catharine E. Bednar, *A Constitutional Analysis of Federal Drug Marketing Regulations and Food and Drug Administration Implementation*, 13 SW. L.J. 531, 542 (1983).

82. *Id.*

83. *Id.*

84. *Id.*

85. *Id.*

86. *Id.*

agents in this country dates back to the New England colonies.<sup>87</sup> However, legal action involving drugs was the exception rather than the rule.<sup>88</sup> Drugs were largely unregulated in the United States until the twentieth century.<sup>89</sup> By comparison, drug regulations were common in European countries at an earlier date.<sup>90</sup> As a result, America became the place to unload substandard and contaminated European drugs in the nineteenth century.<sup>91</sup> Drugs available in the United States were often dangerous due to widespread adulteration.<sup>92</sup>

The first law in the United States regulating drugs on a national level, the Import Drugs Act of 1848,<sup>93</sup> authorized laboratory tests of purity to be performed on imported drugs at the site of entry.<sup>94</sup> The Act also allowed for the detainment and exportation of drugs that failed to meet pharmacopoeial standards.<sup>95</sup> Enforcement of the measure was initially strong, but support dwindled and political backing caused the measure to deteriorate in its effectiveness.<sup>96</sup> Regardless of enforcement, however, the Import Drug Act failed to rid the United States of adulterated medications because it was limited to those substances originating abroad.<sup>97</sup> Legislation was still needed to monitor drugs that were made and marketed domestically.<sup>98</sup>

This meant Americans faced serious risk, because domestically-made nostrums<sup>99</sup> remained the most prevalent form of medication used by Americans

87. In 1630, Nicholas Knopf was sentenced to pay a fine or be whipped for selling "a water of no worth nor value" as a cure for scurvy. Wallace F. Janssen, *The U. S. Food and Drug Law: How It Came; How It Works*, 35 FOOD DRUG COSM. L.J. 132, 133 (1980). Wallace F. Janssen is the historian for the FDA.

88. *Id.*

89. Most colonial laws dealt mainly with foods rather than drugs. *Id.*

90. Wallace F. Janssen, *Outline of the History of U. S. Drug Regulation and Labeling*, 36 FOOD DRUG COSM. L.J. 420, 422 (1981).

91. *Id.* The United States had a customs examination, but only to assure correct valuation for duty purposes. *Id.* at 423.

92. *Id.* at 422.

93. Ch. 70, 9 Stat. 237, 238 (1848) (repealed 1922). The purpose of the Act was to prevent the importation of adulterated and spurious drugs and medicines.

94. Wallace F. Janssen, *Outline of the History of U. S. Drug Regulation and Labeling*, 36 FOOD DRUG COSM. L.J. 420, 423 (1981).

95. *Id.*

96. *Id.*

97. The Act only provided for detention, destruction, or re-exportation of shipments originating abroad that did not meet pharmacopoeial standards. Ch. 70, 9 Stat. 237, 238 (1848) (repealed 1922).

98. Wallace F. Janssen, *Outline of the History of U. S. Drug Regulation and Labeling*, 36 FOOD DRUG COSM. L.J. 420, 423 (1981).

99. A nostrum is a patent medicine or quack remedy. "Nostrums were so common that they were largely taken for granted—a part of the normal American scene. Anyone, no matter how ignorant or unqualified, could go into the drug manufacturing business." *Id.* at 422.

during the nineteenth century.<sup>100</sup> Billed as "patent medicines," hundreds of ineffective elixirs<sup>101</sup> lined the medicine cabinets of an uninformed and unprotected American public.<sup>102</sup> Medications containing such drugs as opium, morphine, and cocaine were sold without restriction at almost every corner apothecary.<sup>103</sup> Innocuous and inert preparations claimed to cure everything from cancer to the common cold.<sup>104</sup> Labels contained neither warnings nor lists of ingredients.<sup>105</sup>

Public sentiment that Congress should enact a law to regulate the drug industry began after the Civil War.<sup>106</sup> Several bills were enacted in response to specific drug-related tragedies,<sup>107</sup> but none had the scope covered by the Pure Food and Drug Act of 1906.<sup>108</sup>

100. *Id.*

101. Nostrums had colorful names such as Kick-a-poo, Indian Sagwa, and Warner's Safe Cure for Diabetes. *Id.*

102. The philosophy of the time for dealing with patent medicines was largely based on the old policy of *caveat emptor* or let the buyer beware. Richard C. Litman & Donald S. Litman, *Protection of the American Consumer: The Muckrakers and the Enactment of the First Federal Food and Drug Law in the United States*, 36 FOOD DRUG COSM. L.J. 647, 647 (1981).

103. Many of the medications sold were positively harmful in their effects. The "headache powers" were vicious habit-forming drugs sold under false, misleading, or incomplete labels. Women and children became addicted to their use in tragic numbers. Mothers doped their babies into insensibility at night with soothing syrups containing opium, cocaine, laudanum and alcohol. The most vicious of the medical frauds was the group that preyed on incurables. Individuals with diseases such as tuberculosis and cancer were usually willing to spend every cent they had to recover their health, and the patent medicine suppliers were quick to supply them with cod liver oil or other dangerous drugs. *Id.* at 652.

104. *Id.*

105. Wallace F. Janssen, *Outline of the History of U. S. Drug Regulation and Labeling*, 36 FOOD DRUG COSM. L.J. 420, 421 (1981).

106. Richard C. Litman & Donald S. Litman, *Protection of the American Consumer: The Muckrakers and the Enactment of the First Federal Food and Drug Law in the United States*, 36 FOOD DRUG COSM. L.J. 647, 648 (1981).

107. Despite the number of measures submitted, very few became law. Between January 20, 1879 and June 30, 1906, when the Pure Food and Drug Act was passed, 190 measures that were designed to protect the consumer from misbranded or adulterated food and drugs were introduced into Congress, a mere eight became law. *Id.* at 661. One of those passing into law was the strongest drug control law ever to that point, the original Biologics Act of 1902, which came in response to the fiasco surrounding the St. Louis Health Department. Twelve children died from tetanus contamination of the diphtheria vaccine that the health department had self-manufactured. Ch. 985, 32 Stat. 286, 296 (1902); Wallace F. Janssen, *Outline of the History of U.S. Drug Regulation and Labeling*, 36 FOOD DRUG COSM. L.J. 420, 425 (1981).

108. Ch. 3915, 34 Stat. 768 (1906) (repealed 1938). The drug provisions have been summarized as follows:

The law, in short, made misrepresentations illegal. It did not force the manufacturer to disclose the contents of his preparation, but if he chose to do so, the government would monitor his accuracy. The producer was obligated to inform the consumer about narcotic content, and he was required to adhere to common standards

The pure food and drug movement was supported by state officials,<sup>109</sup> professional groups,<sup>110</sup> and some members of Congress from the movement's very beginning.<sup>111</sup> However, the regulatory movement was offset by strenuous opposition from many manufacturers, particularly manufacturers of patent medicines, who were then the largest advertisers in the country.<sup>112</sup> Dr. Harvey Washington Wiley was personally responsible for overcoming the resistance created by the drug manufacturers, and the 1906 law is commonly referred to as the Wiley Act.<sup>113</sup>

The 1906 Act was expected to reform patent medicine by outlawing false therapeutic claims,<sup>114</sup> and indeed, the Act did prohibit adulteration and misbranding of these concoctions.<sup>115</sup> However, a serious setback occurred in

if he chose to employ a common name for his product. In addition, no statement could "be false or misleading in any particular"—a high standard. But if the producer wanted to avoid the scope of the law entirely, he could produce a non-narcotic preparation, give it a novel name, and say little about it.

Catharine E. Bednar, *A Constitutional Analysis of Federal Drug Marketing Regulations and Food and Drug Administration Implementation*, 13 SW. U. L. REV. 531, 543 n.72 (1983).

109. Wallace F. Janssen, *Outline of the History of U.S. Drug Regulation and Labeling*, 36 FOOD DRUG COSM. L.J. 420, 426 (1981).

110. This was especially true of the American Pharmaceutical Association and the American Medical Association. *Id.*

111. *Id.*

112. Many of these businessmen felt that they would be put out of business by Federal regulation. Wallace F. Janssen, *The U.S. Food and Drug Law: How It Came; How It Works*, 35 FOOD DRUG COSM. L.J. 132, 134 (1980).

113. In 1883, Dr. Wiley became the chief chemist of the United States Department of Agriculture. It was at this time that Dr. Wiley began his famous crusade to curb the then widespread abuses in the production and sale of drugs, beginning with the expansion of studies by department chemists. Dr. Wiley took the findings of the department to the public as a popular speaker at business organizations and women's clubs. In 1903, Dr. Wiley captured the attention of the nation by establishing a volunteer "poison squad" of young men who agreed to eat only foods treated with measured amounts of chemical preservatives with the object of demonstrating their effects on digestion and health. These experiments piqued the interest of popular song writers, who immortalized them with lyrics such as:

*O, they may get over it but they'll never look the same,  
That kind of bill of fare would drive most men insane.  
Next week he'll give them mothballs, a la Newburgh or  
else plain;*

*O, they may get over it but they'll never look the same.*

By bringing popular attention to the issues of food and drug purity, Dr. Wiley was largely responsible for the almost unanimous vote passing the 1906 Pure Food and Drugs Act. Wallace F. Janssen, *The U. S. Food and Drug Law: How it Came; How it Works*, 35 FOOD DRUG COSM. L.J. 132, 133-35 (1980); Wallace F. Janssen, *Outline of the History of U. S. Drug Regulation and Labeling*, 36 FOOD DRUG COSM. L.J. 420, 420-26 (1981).

114. Gary L. Yingling, *Does Self-Medication Have a Role in Our Society?*, 36 FOOD DRUG COSM. L.J. 604, 611 (1981).

115. Many manufacturers changed their formulas or dropped claims that appeared on the labels of their products that could not be sustained in court. *Id.*

1911. A divided Supreme Court<sup>116</sup> held that although the law prohibited false label statements about the identity or ingredients of the drugs, it did not prohibit false health claims.<sup>117</sup>

President Taft saw the danger created by this loophole and called on Congress to remedy the situation.<sup>118</sup> In response to the President's appeal, Congress passed the Sherley Amendment in 1912,<sup>119</sup> which prohibited false and fraudulent label claims of therapeutic effectiveness of drugs.<sup>120</sup>

Unfortunately, the language of the Amendment required the prosecution to prove that the promoter of a worthless drug had lied deliberately in order to defraud the public, an impossibility in most cases.<sup>121</sup> This loophole remained for twenty-six years, preventing effective enforcement of the amendment.<sup>122</sup> While complying literally with the Sherley Amendment, many drug promoters simply evaded it by transferring the false claims from product labels to advertisements for the drug.<sup>123</sup>

Although the 1906 Act was plagued by inadequacies,<sup>124</sup> another tragedy was necessary to catapult Congress into further action.<sup>125</sup> In 1937, a drug company decided to market the new wonder drug sulfanilamide<sup>126</sup> in liquid rather than the usual tablet form.<sup>127</sup> Due to poor solubility in normal solvents,

116. *United States v. Johnson*, 221 U.S. 488, 495 (1911).

117. In the case of "Dr. Johnson's Mild Combination Treatment for Cancer," Justice Holmes wrote the decision for the Court that held that the defendant could not be prosecuted for making false claims about his product even though he knew that its use would not result in the health claims he made. *Id.* at 495-99.

118. The President said:

There are none so credulous as sufferers from disease. The need is urgent for legislation that will prevent the raising of false hopes of speedy cures of serious ailments by misstatements of facts as to worthless mixtures on which the sick will rely while their disease progresses unchecked.

62 CONG. REC. 2380 (1911).

119. Ch. 352, 37 Stat. 416 (1912).

120. *Id.*

121. Wallace F. Janssen, *Outline of the History of U. S. Drug Regulation and Labeling*, 36 FOOD DRUG COSM L.J. 420, 428 (1981).

122. *Id.*

123. *Id.*

124. The Act operated *post facto*; the Food and Drug Administration lacked the authority for pre-marketing approval and was limited to action after a misbranded or adulterated item was introduced into the marketplace. Dangerous drugs, therefore, had to reach the market before risks became known to consumers or the FDA. Barry S. Roberts & David Z. Bodenheimer, *The Drug Amendments of 1962: The Anatomy of a Regulatory Failure*, 1982 ARIZ. ST. L.J. 581, 583 (1982).

125. *Id.*

126. Sulfanilamide was used to treat acute rheumatic fever, childbed fever and pneumonia. MILTON SILVERMAN & PHILIP R. LEE, PILLS, PROFITS, & POLITICS 6 (1974).

127. *Id.* at 86.

such as water or alcohol, the manufacturer proceeded to dissolve sulfanilamide in di-ethylene glycol.<sup>128</sup> The company failed to perform tests on the safety of the elixir or even to look up the toxicity of the solution in chemical textbooks.<sup>129</sup> People who drank the sulfanilamide elixir died soon afterward.<sup>130</sup> A doctor at the American Medical Association tracked the source of the deaths to kidney damage caused by the di-ethylene glycol.<sup>131</sup> Before all the bottles of the elixir could be tracked down and recalled,<sup>132</sup> at least 107 people, many of them children, had died from the poisonous brew Elixir Sulfanilamide.<sup>133</sup> Due to the limitations of the 1906 law, all that could be done to the manufacturer was to penalize the manufacturer for misbranding the product.<sup>134</sup>

The sulfanilamide calamity provided the impetus necessary for Congress to pass the Food, Drug, and Cosmetic Act of 1938.<sup>135</sup> The new law expanded the scope of the FDA and facilitated tighter enforcement of its regulations.<sup>136</sup> The Act improved the regulations guarding against unsafe drugs by: prohibiting interstate commerce in new drugs unless manufacturers furnished scientific proof to the FDA of the new product's safety prior to marketing; eliminating proof of fraud as a requirement to enjoin false claims for drugs; providing the FDA with specific authority to inspect pharmaceutical production facilities; and authorizing federal courts to restrain violations of the Act by injunctions.<sup>137</sup> Therefore, the primary focus of pharmaceutical regulation in the United States came to be the assured safety of new drugs. This directive remained in effect until

128. Di-ethylene glycol is a key ingredient in automobile anti-freeze. When using this toxic solvent in the Elixir Sulfanilamide, the drug manufacturer added a little coloring and raspberry flavor to enhance the aesthetics of the elixir. *Id.*

129. *Id.*

130. *Id.*

131. The human body metabolizes di-ethylene glycol into kidney-destroying oxalic acid, which in turn causes a slow, agonizing and excruciatingly painful death. *Id.*

132. Part of the difficulty in tracking down all the bottles of the tainted drug came from the fact that drug salesmen lied about their customers, druggists altered their records, and terrified physicians crept into pharmacies at night to destroy their prescriptions. *Id.*

133. *Id.*

134. According to the law, an "elixir" is a solution containing ethyl alcohol. The solvent used, di-ethylene glycol, is not an alcohol, and therefore the product was considered misbranded. The manufacturer later told reporters, "[m]y chemists and I deeply regret the fatal results, but . . . I do not feel there was any responsibility on our part." The chief chemist committed suicide soon after the incident. *Id.* at 87.

135. Ch. 675, § 1, 52 Stat. 1040 (1938) (current version at 21 U.S.C. §§ 301-394 (1988)).

136. Wallace F. Janssen, *Outline of the History of U. S. Drug Regulation and Labeling*, 36 FOOD DRUG COSM. L.J. 420, 429 (1981).

137. *Id.*



1962.<sup>138</sup>

During the decades following World War I, profits for pharmaceutical companies based in the United States soared.<sup>139</sup> The pharmaceutical industry and the FDA enjoyed a rather cordial relationship<sup>140</sup> until, in 1959, Senator Estes Kefauver<sup>141</sup> initiated hearings to investigate monopolistic pricing practices of the pharmaceutical industry.<sup>142</sup> Although the initial thrust of Senator Kefauver's legislation revolved around creating price competition in the pharmaceutical industry,<sup>143</sup> it eventually included a variety of other drug

138. For a detailed history of the 1962 Amendments, see Louis Lasagna, *Congress, The FDA, and New Drug Development: Before and After 1962*, 32 PERSP. BIOLOGY & MED. 322 (1989); Note, *The Drug Amendments of 1962: How Much Regulation?*, 18 RUTGERS L. REV. 101 (1963).

139. "By 1958 the industry's annual budget for research and development was estimated by some to equal that of the National Institutes of Health (\$140,000,000—modest by today's standards of between \$6 and \$7 billion, but very respectable by the standards of the time)." Louis Lasagna, *Congress, The FDA, and New Drug Development: Before and After 1962*, 32 PERSP. BIOLOGY & MED. 322, 323 (1989).

140. *Id.*

141. Senator Kefauver, a populist of independent mind, was one of the initiators of the petition to censure Senator Joseph McCarthy. He also refused to sign the Southern Manifesto against civil rights for blacks, and once cast the lone no vote during debate on a bill outlawing the Communist party in the United States. *Id.*

142. As chairman of the Subcommittee on Antitrust and Monopoly, Senator Kefauver began his historic hearings in 1957 as an investigation of the drug, steel, automobile, and bread industries. S. REP. NO. 448, 87th Cong., 1st Sess. 1 (1961). Between December 1959 and April 1961, this subcommittee concentrated on the economic structure of the drug industry. 107 CONG. REC. 5638 (1961). For the duration of the twenty-six month hearing investigating the drug industry alone, Senator Kefauver's subcommittee generated 12,885 pages of testimony in government records. Louis Lasagna, *Congress, The FDA, and New Drug Development: Before and After 1962*, 32 PERSP. BIOLOGY & MED. 322, 324 (1989).

143. Senator Kefauver advocated compulsory patent licensing for pharmaceutical companies. Barry S. Roberts & David Z. Bodenheimer, *The Drug Amendments of 1962: The Anatomy of a Regulatory Failure*, 1982 ARIZ. ST. L.J. 581, 584 (1982). Although the Kefauver hearings were not intended to increase the public's protection from unsafe drugs, other forces were concerned with improving consumer protection. In 1969, President Eisenhower's Secretary of Health, Education and Welfare, Arthur Flemming, requested that the National Academy of Sciences National Research Council review FDA procedures in an effort to protect the public health. Note, *The Drug Amendments of 1962: How Much Regulation?*, 18 RUTGERS L. REV. 101, 103 (1963). In January of 1961, Congresswoman Sullivan introduced H.R. 1235, an omnibus food, drug and cosmetic bill, which attempted to close all major loopholes in the 1938 Act. H.R. 1235, 87th Cong., 1st Sess., 107 CONG. REC. 61 (1961). The House of Representatives' support of consumer protection was not mirrored by the Senate, which held economics as its priority. Abraham Ribicoff, President Kennedy's Secretary of Health, Education and Welfare, endorsed the general approach of S. 1552, Kefauver's bill, but expressed concerns that S. 1552 failed to close up significant loopholes of the 1938 bill that the Secretary felt were important concerns to his department. Furthermore, Secretary Ribicoff thought that the patent and anti-trust provisions of S. 1552 were outside the scope of his office. Note, *The Drug Amendments of 1962: How Much Regulation?*, 18 RUTGERS L. REV. 101, 104 (1963). Not surprisingly, after its introduction, S. 1552 was vehemently opposed by the pharmaceutical industry. *Id.* at 106. This prompted the Kefauver subcommittee to launch a new

regulation reforms, the most important of which required pre-marketing proof of a drug's efficacy for its intended use.<sup>144</sup> The FDA now imposes a two-step burden of proof before approval of a new prescription drug: the drug must be shown to be both safe and effective before it can be released into the market.<sup>145</sup>

As with the 1906 and the 1938 enactments, the 1959 efforts to revise the drug laws faced vigorous opposition in Congress.<sup>146</sup> But just as the legislation seemed sure to die for lack of congressional support, the effort received a life-saving boost from yet another drug disaster: the use of thalidomide<sup>147</sup> by pregnant women.<sup>148</sup> Senator Kefauver's staff collected extensive information on thalidomide that they strategically released, creating public outcry for more stringent drug regulation.<sup>149</sup> Congress responded by enacting the Drug Amendments of 1962.<sup>150</sup> It is ironic that the thalidomide scandal, which vividly illustrated the need for increased safety measures, prompted the 1962

round of hearings which lasted from July 5, 1961 to Feb 7, 1962, which were marked by many testimonials from affected and interested parties. *Id.* at 108. In May, 1961, Congressman Celler introduced the House counterpart of S. 1552, dealing with quality control, drug effectiveness, new drug clearance procedures, factory inspections, official names, advertising, and anti-biotic certification. H.R. 6245, 87th Cong., 1st Sess., 107 CONG. REC. 5691 (1961). While the Senate and the House deliberated their separate bills, the thalidomide crisis arose. Sensing the public's outrage over this tragedy, President Kennedy made the recommendation that the House bill be incorporated into the Kefauver bill. Consequently, the amended S. 1552 was passed on August 23, 1962. 108 CONG. REC. 17,422 (1962).

144. Catharine E. Bednar, *A Constitutional Analysis of Federal Drug Marketing Regulations and Food and Drug Administration Implementation*, 13 SW. U. L. REV. 531, 544 (1983).

145. *Id.*

146. 108 CONG. REC. 16,413 (1962).

147. Introduced by a German firm, Chemie-Grünenthal, thalidomide quickly won acceptance as one of the safest sedatives available. Thalidomide produces a normal, refreshing sleep without the morning grogginess usually associated with sedatives. Thalidomide was widely administered to fretful infants. It was thought to be free from any significant side effects and seemed to be virtually suicide-proof. MILTON SILVERMAN & PHILIP R. LEE, *PILLS, PROFITS & POLITICS* 94 (1974).

148. Use of thalidomide in Europe by pregnant women resulted in 3,500 to 5,000 cases of a severe birth defect known as phocomelia, in which the baby's feet and hands are attached close to its body like flippers. S. REP. NO. 1744, 87th Cong., 2nd Sess. 40 (1962). Although it was not approved by the FDA for marketing in the United States, thalidomide had been distributed by William S. Merrell Co., thalidomide's manufacturer, to physicians for investigational purposes. HOUSE SUBCOMM. ON SCIENCE, RESEARCH AND TECHNOLOGY OF THE COMM. ON SCIENCE AND TECHNOLOGY, 96TH CONG., 2ND SESS., *REPORT ON THE FOOD AND DRUG ADMINISTRATION'S PROCESS FOR APPROVING NEW DRUGS* 8 (Comm. Print 1980). According to an FDA survey, thalidomide was distributed to 3,897 women of child-bearing age in the United States. Nine gave birth to malformed children. Arthur H. Hayes, *Food and Drug Regulation After 75 Years*, 246 JAMA 1223, 1224 (1981).

149. 108 CONG. REC. 23,179-80 (1962).

150. Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (codified as amended at 21 U.S.C.A. §§ 301-394 (West Supp. 1992)).

Amendments, which dealt primarily with issues of drug effectiveness.<sup>151</sup> In fact, members of the 1962 Congress<sup>152</sup> also recognized that the 1962 Amendments provided no certainty of protection for the American public against future thalidomide-like disasters.<sup>153</sup>

This historical investigation of drug regulation in the United States illustrates the nature of this country's regulatory efforts, namely that legislation occurs in an attempt to allay the public's fears stemming from an immediate and narrow crisis. Regulations are vehemently enforced during the period of the crisis, but once the public's fears fade, so does governmental interest. The AIDS crisis has led to the promulgation of the latest set of FDA reforms in an effort to calm the public's fears.<sup>154</sup>

#### IV. PROBLEMS WITH THE 1991 DRUG APPROVAL REFORMS

##### A. The 1991 Drug Approval Reforms

The FDA has recently implemented the most sweeping changes in the past thirty years in the prescription drug approval process.<sup>155</sup> The President's Council on Competitiveness has promulgated eleven specific reforms<sup>156</sup> in an attempt to speed up the FDA's approval process for new prescription drugs. These include: the use of external review,<sup>157</sup> expanded use of advisory committees,<sup>158</sup> an expanded role for Institutional Review Boards,<sup>159</sup> flexible

151. Barry S. Roberts & David Z. Bodenheimer, *The Drug Amendments of 1962: The Anatomy of a Regulatory Failure*, 1982 ARIZ. ST. L.J. 581, 584 (1982).

152. See 108 CONG. REC. 16,412 (1962) (remarks of Representative Sullivan).

153. Max Sherman & Steven Strauss, *Thalidomide: A Twenty-Five Year Perspective*, 41 FOOD DRUG COSM. L.J. 458, 464 (1986).

154. The FDA has come under increasing attack in recent years for its languid pace of bringing new and important drugs to the marketplace, particularly in the context of the growing AIDS epidemic. See Marlene Cimonis, *FDA Likely to Speed Approval of New Drugs*, LOS ANGELES TIMES, Nov. 8, 1991, at A1.

155. *FDA Set to Speed Drug Approvals*, CHI. TRIB., Nov. 8, 1991, § 1, at 8.

156. Recommendations, *supra* note 13, at 43,617.

157. External review entails the use of experts outside the government to conduct clinical reviews for Investigational New Drugs. The goal of external review is to lessen the need for the FDA to conduct its own investigation on the clinical data. *Id.* at 43,620.

158. The FDA will be using advisory committees to assist reviewing divisions in monitoring the progress of New Drug Applications (NDAs). Advisory committee expertise will be used in the early stages in development and execution of clinical testing. *Id.* at 43,621.

159. Institutional Review Boards (IRBs) provide assistance to the FDA in designing and reviewing clinical studies, especially in respect to ethical issues and informed consent. This proposition would allow IRBs to make decisions regarding initial human testing. *Id.*

interpretation of the efficacy standard,<sup>160</sup> accelerated approval,<sup>161</sup> expanded use of foreign data and recognition of foreign approvals in the United States,<sup>162</sup> enhanced computerization,<sup>163</sup> establishment of a classification system for application priorities,<sup>164</sup> the use of internal systems of accountability,<sup>165</sup> reduction of excessive liability costs,<sup>166</sup> and the direction of staff and financial resources toward new drug review.<sup>167</sup>

Most of these recommendations have been adopted by the FDA as official policy<sup>168</sup> and are believed by some to be the method to finally clear the FDA's

160. This calls for the FDA to make a deliberate effort to interpret the statutory requirement of efficacy in a manner which factors into it the risks to human life and health that may result from delaying the introduction of the new drug. This means that instead of applying the same strict standard to all new drugs, the FDA will balance the need for the drug against the drug's effectiveness. *Id.*

161. The FDA will reduce the number of clinical studies required prior to a new drug's approval as well as the amount of time the FDA takes to approve drugs which are used to treat life-threatening, very serious or severely debilitating diseases. *Id.* at 43,622.

162. This calls for the FDA to develop with foreign countries: common standards for clinical studies; common format for submission of drug approval applications; common sets of requirements for animal testing; criteria for plant inspections and good manufacturing practices; and a reciprocity for approvals. It also calls for the FDA to accept foreign data used for approval of drugs whenever possible. *Id.* at 43,623.

163. The FDA will develop a plan to fully computerize new drug applications. *Id.* at 43,624.

164. The FDA will adopt a new system of classification for all new drug applications. The new system will consist of two categories: "routine" and "expedited." In each category, the priority of review will be based on a "first in, first reviewed" principle. The FDA's current system prioritizes drugs having the greatest potential therapeutic benefits. The existing system does not consider the economic impact of a drug. *Id.* at 42,524-25.

165. The FDA will adopt internal management systems to: help monitor every application's progress for each product submitted; and measure the application's progress against a timetable based on statutory standards; and substantially reduce the use of clinical holds of investigational new drug applications as well as closely monitoring the duration of clinical holds. The term "clinical hold" refers to the authority of the FDA to delay for reasons of safety the beginning of early clinical trials conducted on investigational new drugs. *Id.* at 43,625.

166. The administration supports efforts to exempt drug manufacturers from punitive damages when the FDA has approved the drug. *Id.*

167. To improve the capability of the institution to review new drugs, the FDA will prioritize first the hiring of new drug review staff in the areas most in need of staffing, especially in the biotechnology area. *Id.* at 43,626.

168. The FDA issued new guidelines on the process of approving drugs. These guidelines substantially incorporate the recommendations from the Council on Competitiveness. Two of the most controversial suggestions were dropped from the new guidelines. The suggestions not included involve a plan to fully coordinate the United States' drug approval with foreign countries including acceptance of foreign approvals for new drugs. The other unaccepted suggestion would have enabled individuals outside the FDA to authorize initial small-scale, human safety testing of new drugs. *New FDA Approval Guidelines Set*, FACTS ON FILE WORLD NEWS DIGEST, May 14, 1992, at 353, C1.

clogged approval system of new prescription drugs.<sup>169</sup> The omnibus goals adopted by the Administration declare that by 1994 the FDA will have reduced the average development and approval time for all new drugs by 3.75 years, will have reduced the average development time for therapies used to treat serious or life threatening diseases by forty-five percent,<sup>170</sup> and will have reduced the average development for all other therapies by twenty-five percent.<sup>171</sup>

### B. Opposition

Not everyone is as optimistic as Vice President Quayle about these reforms, however. Senator Edward Kennedy, Congressman John Dingell, and Congressman Henry Waxman wrote a joint letter to the Commissioner of Food and Drugs asserting that the new recommendations would cause the FDA to abdicate its statutory responsibility to make key decisions on the safety and efficacy of drugs.<sup>172</sup> Although the legislators endorsed the intent of the changes, they said the agency's plan to contract with external experts to aid in reducing the backlog of new drug applications "would undermine the very purpose for which [the FDA] was created and that it is uniquely qualified to fulfill--the protection of the American public from unsafe and ineffective drugs."<sup>173</sup> Other members of Congress have also expressed concern over the new reforms.<sup>174</sup>

Charles Edwards, former FDA Commissioner, agrees with the congressmen that the reforms will diminish the autonomy of the FDA. According to Mr.

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169. Vice President Quayle commented:

The Administration's major reforms in the FDA's drug approval process will cut years off the review process. They will also save millions of lives and billions of dollars. Under these reforms, patients with serious and life threatening diseases will benefit from earlier access to important new drugs. Unnecessary regulatory burdens will be eased.

Recommendations, *supra* note 13, at 43,618.

170. The FDA will have reduced the average development time of therapies for serious diseases by approximately five and one half years. *Id.*

171. The FDA will have reduced the average development time of other therapies by approximately seven years. *Id.*

172. The congressmen stated that by allowing private contractors to review the safety and efficacy of drugs, permitting the United States to accept drug approvals of foreign governments, and using private review boards, the FDA was raising serious concerns, including the prospect of inconsistent standards and the possibility that commercial interests might override scientific objectivity. Council on Competitiveness Recommendations Prompt Concern, [1990-91 Transfer Binder] Food Drug Cosm. L. Rep. (CCH) ¶ 42,611, at 1520 (March 30, 1992).

173. Malcolm Gladwell, *Critics Say New FDA Procedures for Approving Drugs Would Weaken Agency*, WASH. POST, Nov. 14, 1991, § 1, at A3.

174. Congressman Ted Weiss has also expressed misgivings about several sections of the reforms. Ronald Begley, *The Jury Is Still Out On FDA Reforms*, CHEMICAL WK., Aug. 12, 1992, at 24.

Edwards, a strengthening rather than a weakening of the FDA is the only means by which the drug approval process can be effectively accelerated.<sup>175</sup> Dr. Sidney Wolfe, director of the Public Citizen Health Research Group, also expresses concern that the new reforms could possibly yield a significant risk because of the dangers that may have been overlooked in the abbreviated process without a balancing benefit to patients.<sup>176</sup>

### C. Weaknesses in the 1991 Reforms

#### 1. Time Delays

The first three reforms all call for expanded use of external review. The FDA will contract with experts to assist in the clinical review of new drugs,<sup>177</sup> extend its use of advisory committees,<sup>178</sup> and augment the role of Institutional Review Boards<sup>179</sup>. Under the current FDA system, drug sponsors prepare

175. The head of a recent panel to reform the FDA, Charles Edwards, calls the new reforms "a lot of nonsense." *Id.*

176. Dr. Sidney Wolfe recognizes the potential benefits to pharmaceutical companies because their products would be on the market earlier, giving them a more competitive advantage over other drugs. It seems ironic for the FDA to put forth changes that will promise greater benefit to industry than to the health of the American public. Marlene Cimon, *FDA Likely to Speed Approval of New Drugs*, LOS ANGELES TIMES, Nov. 8, 1991, at A1.

177. Qualified external review organizations will be contracted by the FDA to conduct clinical reviews from classes of pharmaceuticals where backlogged applications have been pending more than the statutory 180 days. This external review organization will certify that it has evaluated the data, as well as give an opinion as to whether the data satisfies the statutory requirements of safety and efficacy. Although the FDA need not conduct its own analyses of the data, it retains the right to fully review the clinical data of the external reviews as well as the right to perform its own review when there is an indication that the external review has not been properly performed. Moreover, the FDA will retain its authority to make the final decision to approve the drug if it meets the statutory requirements for safety and efficacy. The FDA will pay for external review from discretionary funds. It will certify and monitor three or more external organizations, which it deems qualified, to conduct an independent review of clinical data. The external review builds upon current practice; the FDA contracts with outside experts to assist in the clinical review of new drugs, as well as relying on Institutional Review Boards (IRBs) to grant Investigational New Drugs (INDs). Recommendations, *supra* note 13, at 43,620.

178. The FDA will phase in the expanded use of advisory committees to assist in monitoring the progress of New Drug Applications and Product License Applications for biologics. Advisory committees will be used to advise drug sponsors about the design and the number of clinical studies necessary to test Investigational New Drugs (INDs). Advisory committee expertise will, therefore, be tapped by the FDA earlier in the development and the execution of human clinical testing. *Id.* at 43,621.

179. Previously, both the FDA and the Investigational Review Board had to review the Investigational New Drugs before continuing beyond initial testing. Reform number three, however, permits sponsors of new drugs to submit their applications for INDs to the appropriate IRB for approval without requiring additional agency review. *Id.* at 43,621.

data about the technical sections<sup>180</sup> of New Drug Applications (NDAs). This data includes summaries of each section of the application as well as an overall summary of the application provided by the pharmaceutical industry.<sup>181</sup> These data are similar to the reviews that will be generated by external experts under the new reforms.<sup>182</sup>

Although the summaries from drug sponsors follow standard guidelines,<sup>183</sup> they are presently given little attention by FDA reviewers.<sup>184</sup> FDA reviewers consider the summaries produced by outside sources as impersonal and colorless in style, lacking in detail, exhibiting discordance between summaries and test reports or results, failing to address problem areas candidly, lacking expertise in writing style and argument, and possibly biased.<sup>185</sup> Furthermore, FDA reviewers prefer to create their own impressions of the New Drug Application (NDA) from their individual study of the reports or by the time-consuming method of re-analyzing test results.<sup>186</sup>

It is unlikely that the 1991 Reforms will have any effect on these common practices by FDA reviewers. The Reforms fail to address the grounds for objection by which FDA reviewers justify their frequent rejection of external data, with the possible exception of sponsor bias. Under the Reforms, the FDA retains the right to fully review the clinical data of an external review<sup>187</sup> and will certainly continue to exercise that right.

The Commissioner and the staff of the FDA ultimately bear the responsibility for their approval decisions.<sup>188</sup> The role of external experts must legally remain an advisory one.<sup>189</sup> If an FDA official approves a drug which later proves to be unsafe,<sup>190</sup> that official is the one who is held

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180. Technical sections include clinical or human data, pharmacology-toxicology or animal data, chemistry, statistics, biopharmaceutics, and (for antibiotics) microbiology. Barrett Scoville, *Shifting the Burden: Restructuring the Drug Review Process*, 49 CLINICAL PHARMACOLOGY & THERAPEUTICS 229, 230 (1991).

181. *Id.*

182. *Id.*

183. The standard process consists of a reviewer documenting the evaluation of each section of the application with a ten to sixty page written report. *Id.*

184. *Id.*

185. *Id.*

186. The reviewers at the FDA spend weeks, even months, resummarizing material that has already been summarized. Barrett Scoville, *Shifting the Burden: Restructuring the Drug Review Process*, 49 CLINICAL PHARMACOLOGY & THERAPEUTICS 229, 230 (1991).

187. Recommendations, *supra* note 13, at 43,620.

188. Louis Lasagna, *Congress, the FDA, and New Drug Development: Before and After 1962*, 32 PERSP. BIOLOGY & MED. 322, 337 (1989).

189. *Id.* at 336.

190. For example, thalidomide.

responsible for releasing that drug to the public.<sup>191</sup> On the other hand, if the official errs on the side of safety and withholds approval, no one learns of the loss, let alone who is responsible for the loss to society of a beneficial new drug.<sup>192</sup>

A recent Supreme Court decision<sup>193</sup> against the FDA provides even further incentive for the FDA to become even more cautious, rigorous, and time-consuming in its approval of new prescription drugs. In *Berkovitz v. United States*,<sup>194</sup> the Supreme Court limited liability protection for a government agency that failed to comply with its own regulatory standards.<sup>195</sup> The FDA claimed that the Federal Tort Claims Act (FTCA)<sup>196</sup> protected the FDA on the grounds that their approval of the vaccine constituted "discretionary duty," therefore making the FDA exempt from liability in the suit.<sup>197</sup> The

191. Louis Lasagna, *Congress, the FDA, and New Drug Development: Before and After 1962*, 32 PERSP. BIOLOGY & MED. 322, 336 (1989).

192. Former FDA Commissioner Alexander Schmidt aptly expressed this dilemma faced by the FDA:

For example, in all the FDA's history, I am unable to find a single instance where a congressional committee investigated the *failure* of the FDA to approve a new drug. But, the times when hearings have been held to criticize our approval of new drugs have been so frequent that we aren't able to count them. . . . The message of FDA staff could not be clearer. Whenever a controversy over a new drug is resolved in favor of approval, the Agency and the individuals involved likely will be investigated. Whenever such a drug is disapproved, no inquiry will be made. The congressional pressure for our *negative* action on new drug applications is, therefore, intense.

HAROLD GRABOWSKI, DRUG REGULATION AND INNOVATION 76 (1976) (quoting speech by Alexander Schmidt before the National Press Club, Washington, D.C. (October 29, 1974)). Nor can the FDA be overly cautious, according to congressional standards. When the FDA approved propranolol for the treatment of angina in 1973, the drug had already been approved for this use in Britain for seven years. Propranolol was so effective in the treatment of angina that United States physicians had been prescribing propranolol for the treatment of angina even before FDA approval. In spite of rare international consensus on propranolol's efficacy in treating angina, a congressional oversight committee severely chastised the FDA for approving the drug without sufficient evidence of effectiveness even though the FDA had relied upon over a dozen studies in approving the NDA. See Louis Lasagna & William M. Wardell, *The FDA, Politics, and the Public*, 232 JAMA 141, 141 (1975); *Use of Advisory Committees by the Food and Drug Administration: Hearings Before the Subcomm. on Intergovernmental Relations of the House Comm. on Government Operations*, 93rd Cong., 2nd Sess. (1974).

193. *Berkovitz v. United States*, 486 U.S. 531 (1988).

194. *Id.*

195. A child contracted a severe case of polio after ingesting an oral vaccine for polio. The child sued the Bureau of Biologics of the FDA for releasing that particular batch of vaccine to the public. *Id.* at 533.

196. 28 U.S.C. § 1346(b), 2671-2680 (1988).

197. The FTCA generally authorizes suits against the United States

for monetary damages . . . for injury or loss of property, or personal injury or death caused by the negligent or wrongful act or omission of any employee of the Government while acting within the scope of his office or employment, under circumstances where



Court, however, held that the discretionary function exception of the FTCA does not apply when a federal statute, regulation, or policy specifically prescribes a course of action for an employee to follow.<sup>198</sup>

Because FDA employees follow regulations governing the drug approval process, they remain legally liable for consequential mishaps occurring from their actions.<sup>199</sup> When a suit charges an agency with failure to act in accordance with a mandatory directive, liability will attach.<sup>200</sup> This precedent dictates even more apprehensive approval of new drugs by the FDA, resulting in a greater time delay in bringing a new prescription drug to market in the United States.

Reform number three,<sup>201</sup> which calls for the expanded use of Institutional Review Boards (IRB), merely reiterates present FDA policy. The FDA's use of IRBs to review and approve applications for Investigational New Drugs (INDs) has been in effect since 1987.<sup>202</sup> However, the research community<sup>203</sup> failed to respond to the FDA's opportunities to become part of a review board because researchers are apprehensive of potential liability problems stemming from their involvement with the FDA.<sup>204</sup> Top FDA officials doubt whether researchers will respond any more enthusiastically to an expansion of opportunities to join IRBs because liability still exists.<sup>205</sup>

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the United States, if a private person, would be liable to the claimant in accordance with the law of the place where the act or omission occurred.

28 U.S.C. § 1346(b) (1988).

The Act includes a number of exceptions to this broad waiver of sovereign immunity. The exception relevant to this case provides that no liability shall lie for

[a]ny claim . . . based upon the exercise or performance or the failure to exercise or perform a discretionary function or duty on the part of a federal agency or an employee of the Government, whether or not the discretion involved be abused.

28 U.S.C. § 2680(a) (1988).

198. *Berkowitz v. United States*, 486 U.S. 531, 539 (1988).

199. *Id.* at 538.

200. *Id.*

201. Recommendations, *supra* note 13, at 43,621.

202. *IRBs Would Have Authority to Approve Investigational New Drug Applications Under Competitive Council Plan*, FDC REP. (THE BLUE SHEET), Nov. 20, 1991, at 6.

203. The President's Council for Competitiveness recommends that the FDA choose its outside reviewers from the qualified experts in the research community, identified as large statistical research companies, private industry consulting organizations, universities (coalitions of pharmacy, medical, and public health schools), FDA and/or drug industry retirees, private physicians and other experts experienced in conducting clinical investigations, and new private entities. *Id.*

204. *Id.*

205. Although one of the new reforms is aimed at reducing excess liability costs, this reduction applies only to pharmaceutical manufacturers, not the reviewers. Recommendations, *supra* note 13, at 43,625.

The use of external experts by the FDA has also been realistically inhibited by the restrictive interpretation of the federal conflict-of-interest statute<sup>206</sup> that prohibits government employees from participating in decisions in which they have a financial interest. This extends to the FDA's Advisory Committee members, and would therefore significantly reduce the field of experts available to fill advisory positions proposed by the 1991 reforms because many such experts are employed by pharmaceutical companies.<sup>207</sup>

Under the new reforms to be implemented by the FDA, FDA personnel remain ultimately and legally responsible for their decision to approve new drugs.<sup>208</sup> Cases such as *Berkovitz*<sup>209</sup> ensure continuation of the slow pace of the FDA in approving new prescription drugs. The cost of releasing an unsafe or unacceptable drug into the marketplace is high, and the FDA staff will logically continue to judge the data they receive with caution. Not only does liability ensure that FDA staff members move along conservative paths toward new drug approval, but it also acts to repel the research community from involvement in the drug approval process.<sup>210</sup>

The FDA has already decided to reject the proposal that allowed IRBs to authorize small-scale, human safety testing of new drugs.<sup>211</sup> This proposal met such strong opposition that the FDA decided against implementing a plan that removed responsibility from the FDA in new drug trials involving human subjects.<sup>212</sup>

The new reforms lack any relief from liability, which will help to ensure that the individuals responsible for making the decisions at the FDA will

206. 18 U.S.C. § 208 (1988).

207. See PROBLEMS INVOLVING FEDERAL CONFLICT OF INTEREST RESTRICTIONS ON MEMBERS OF FDA ADVISORY COMMITTEES AND AGENCY OFFICIALS (Center for the Study of Drug Development, Publication No. PS 8032 (1980)).

208. Louis Lasagna, *Congress, the FDA, and New Drug Development: Before and After 1962*, 32 PERSP. BIOLOGY & MED. 322, 337 (1989).

209. See *supra* notes 193-200 and accompanying text.

210. Some members of the research community feel that the FDA would be exposing members of the IRBs to substantial liability if the drug approved by the IRB was later found to have harmful effects. *IRBs Would Have Authority to Approve Investigational New Drug Applications Under Competitive Council Plan*, FDC REP. (THE BLUE SHEET), Nov. 20, 1991, at 6.

211. Malcolm Gladwell, *FDA Implements Changes in Drug Approval Process*, WASH. POST, April 10, 1992, at A2.

212. FDA Oncology and Pulmonary Drugs Division Medical Reviewer, Grant Williams, maintained that independent reviews of initial human testing by IRBs would endanger the safety of the subjects. Mr. Williams found that in numerous cases IRBs overlooked many dangers that were found by the FDA when intervening in the IRBs' reviewing process. *IRB Review of Investigational New Drug Applications Would Be Dangerous, FDA Medical Reviewer Consents*, FDC REP. (THE BLUE SHEET), Dec. 4, 1991, at 3.

continue to spend valuable time, money, and other resources needlessly reproducing summaries and reviews in an effort to remain as faultless as possible.<sup>213</sup> The 1991 FDA reforms fail to adequately address these issues and these pressing problems will, therefore, continue unabated.

Another weakness not addressed by the 1991 Reforms is the sheer bulk of paperwork involved in the approval process for new prescription drugs.<sup>214</sup> An application for a new drug can be 100,000 pages or more.<sup>215</sup> Not only do the reforms fail to reduce the length, in time and pages, of the drug application process, but reforms, such as those creating a classification system and establishing an internal system of accountability,<sup>216</sup> will invariably add to the huge quantity of paperwork faced by FDA officials. The Reforms promise to reduce the average approval time by 3.75 years,<sup>217</sup> but because most of the time-consuming obstacles have been left in place, it is unlikely that such progress will be made.<sup>218</sup>

## 2. Costs

A very practical limitation in the 1991 FDA reforms is the issue of economics. The only reform directly addressing the issue of cost is the reform calling for decreased liability costs.<sup>219</sup> However, this reform may be the weakest of them all because it calls for support to pass Senate Bill 640, the "Products Liability Fairness Act."<sup>220</sup> Senate Bill 640 includes a provision which would exempt drug manufacturers from punitive damages if a drug had FDA approval.<sup>221</sup> A simple call for support of a Senate bill surely falls short of real reform. Nor do punitive damage awards account for the bulk of costs incurred by drug sponsors bringing a new prescription drug to market.

The current system of prescription drug approval is not only costly to manufacturers,<sup>222</sup> but the cumbersome method followed by the FDA is also

213. See *supra* notes 180-186 and accompanying text.

214. Recommendations, *supra* note 13, at 43,624-25.

215. David Hanson, *Pharmaceutical Industry Optimistic About Improvements at FDA*, 70 CHEMICAL & ENGINEERING NEWS 28, 28 (1992). This is an astounding amount of information, especially when one considers that the Code of Federal Regulations, complete with 196 paperback volumes, contains only 122,090 pages. BERNARD SCHWARTZ, ADMINISTRATIVE LAW 168 (3rd ed. 1991).

216. Recommendations, *supra* note 13, at 43,624-25.

217. *Id.* at 43,618.

218. See *supra* notes 177-200 and accompanying text.

219. Recommendations, *supra* note 13, at 43,625.

220. *Id.*

221. S. 640 would exempt drug manufacturers from punitive damages in a drug product liability case when the drug has FDA approval. *Id.*

222. See *supra* notes 25-39 and accompanying text.

costly for the agency itself. Several reforms<sup>223</sup> require expenditure of nonexistent funds. For instance, the Gramm-Rudman Act has forced the FDA to lay off over 1200 staff members<sup>224</sup> from 1979 to 1986.<sup>225</sup> The FDA did not regain its previous level of staff until 1991, when the number of FDA employees rose to 8400.<sup>226</sup> Although Congress has proposed to increase the 1993 FDA budget to \$797 million,<sup>227</sup> numerous monetary problems remain.<sup>228</sup> Over the past five years Congress has heaped new responsibilities on the FDA without providing the increase of funds necessary to carry out these greater duties.<sup>229</sup>

Meanwhile, areas needing attention by the FDA, such as biotechnology innovation are burgeoning.<sup>230</sup> The FDA has managed to approve only fourteen biotechnical medicines in the past nine years.<sup>231</sup> There are currently over 130 biotechnical medicines being tested, revealing a growth of over sixty percent in the last four years.<sup>232</sup> Furthermore, the FDA approved only a single medicine produced by biotechnology in 1990, and only two biotechnical medications in 1991.<sup>233</sup> Congress has recently sent a message to the FDA that increased surveillance in the drug and device industries is needed.<sup>234</sup>

223. Reforms such as those calling for enhanced computerization of the FDA's drug approval process, direction of human and financial resources toward new drug review, establishment of internal sources of accountability, and expansion of external review all require expenditure of funds. Recommendations, *supra* note 13, at 43,620-26.

224. This figure constituted fifteen percent of the total FDA staff. Gerald F. Meyer, *The Impact of Gramm-Rudman Legislation on FDA*, 42 FOOD DRUG COSM. L.J. 155, 155 (1987).

225. *Id.* The FDA staff fell from over 8000 employees in 1979 to less than 7000 in 1987. Ann Gibbons, *Can David Kessler Revive the FDA?*, 252 SCIENCE 200, 203 (1991).

226. *Id.*

227. *FDA Human Drugs Program Allocated \$204 Mil. in FY 1993, Up 4.4%, Under Bush Administration Request; FDA's Total Budget Set at \$797 Mil. for 1993*, FDC REP. (THE PINK SHEET), Feb. 3, 1992, at 13.

228. Gerald F. Meyer, *The Impact of Gramm-Rudman Legislation on FDA*, 42 FOOD DRUG COSM. L.J. 155, 156 (1987).

229. In the past, Congress has required that the FDA hasten approvals of more generic medicines and drugs for rare diseases. Unfortunately, when Congress did consider giving the FDA more money, the General Accounting Office stated that poor accounting methods within the FDA made it impossible to determine where the resources were needed most. Ann Gibbons, *Can David Kessler Revive the FDA?*, 252 SCIENCE 200, 200 (1991).

230. David Hanson, *Pharmaceutical Industry Optimistic About Improvements at FDA*, 70 CHEMICAL & ENGINEERING NEWS 28, 29 (1992).

231. *FDA Slow on Biotechnology Approvals*, 69 CHEMICAL & ENGINEERING NEWS 14, 14 (1991).

232. *Id.*

233. David Hanson, *Pharmaceutical Industry Optimistic About Improvements at FDA*, 70 CHEMICAL & ENGINEERING NEWS 28, 29 (1992).

234. William D. Appler & Gaile L. McMann, *FDA in the 1990s*, NS30 AM. PHARMACY 27, 32 (1990).

Although the 1991 Reforms propose that the first priority of FDA resources will be dedicated to new drug approval,<sup>235</sup> substantial resources will actually have to be diverted away from the drug approval process and channeled toward traditional oversight and enforcement activities.<sup>236</sup> With such tight budgetary constraints and ever increasing responsibilities, the FDA is unlikely to be capable of meeting the financial demands of the 1991 Reforms.

### 3. Safety

The FDA has already rejected the 1991 Drug Approval Reform's suggestion to accept foreign drug approvals as primary evidence of a new drug's safety.<sup>237</sup> However, the idea of harmonizing the FDA drug approval process with other countries may be a possibility.

A 1991 modification calls for the FDA to place a "very high priority" on harmonizing the FDA drug approval system with other industrialized countries in order to facilitate the FDA's recognition of foreign approval of new drugs.<sup>238</sup> The reforms also suggest that when reviewing a drug approved elsewhere the FDA should capitalize on the resources spent by other countries and, whenever possible, forego unnecessary repetition of clinical trials.<sup>239</sup> However, this reform represents no change from past FDA procedure.<sup>240</sup> There has never been any regulation barring the use of foreign research data in the United States.<sup>241</sup>

What has prevented the FDA from utilizing foreign data in the past has been the FDA's concern for safety.<sup>242</sup> As a matter of policy, the FDA, with certain exceptions, requires at least one clinical investigation to be performed by a competent and recognized domestic investigator.<sup>243</sup> Almost fifty percent of the NDAs for new molecular entities approved between 1974 and 1978 contained reports of studies done in other countries.<sup>244</sup> The FDA generally accepts foreign trials without much concern if they merely confirm domestically derived

235. Recommendations, *supra* note 13, at 43,626.

236. William D. Appler & Gaile L. McMann, *FDA in the 1990s*, NS30 AM. PHARMACY 27, 32 (1990).

237. *New FDA Approval Guidelines Set*, FACTS ON FILE WORLD NEWS DIGEST, May 14, 1992, at 353, C1.

238. Recommendations, *supra* note 13, at 43,623.

239. *Id.*

240. Jerome A. Halperin, *From Investigation to Marketplace: Moving Drugs Through the System*, 36 FOOD DRUG COSM. L.J. 166, 169 (1981).

241. *Id.*

242. *Id.*

243. *Id.*

244. *Id.*

research data.<sup>245</sup>

However, problems arise when foreign clinical data is pivotal to FDA approval.<sup>246</sup> Despite the FDA's public posture regarding foreign trial data, the FDA rarely accepts foreign data as primary evidence, even when the foreign trials appear absolutely impeccable.<sup>247</sup> The FDA resists acceptance of scientific data even from most European countries,<sup>248</sup> and it is standard policy for the FDA to require randomized, controlled clinical trials to be repeated within the United States before a new drug can be approved.<sup>249</sup> Consensus among experts is rare, but scientists and leaders of the pharmaceutical industry strongly agree that such replication is wasteful and undesirable.<sup>250</sup> However, obstacles inherent to the attitudes of FDA staff members, such as those discussed in this section, prevent the FDA from more readily accepting foreign research data.

The FDA identifies numerous safety barriers to the use of foreign research data, including the Agency's lack of familiarity with foreign languages,<sup>251</sup> Europe's shorter historical commitment to modern, controlled, high-quality

245. Louis Lasagna, *On Reducing Waste in Foreign Clinical Trials and Postregulation Experience*, 40 CLINICAL PHARMACOLOGY & THERAPEUTICS 369, 370 (1986).

246. *Id.*

247. Louis Lasagna, *Congress, The FDA, and New Drug Development: Before and After 1962*, 32 PERSP. BIOLOGY & MED. 322, 337 (1989). The quality of much foreign data is high because the pharmaceutical industry is dominated by multinational corporations who recognize the importance of the United States as a market, providing strong incentives for major companies to guarantee that trials conducted in other countries will meet the standards of the FDA. In spite of this, the FDA has continually refused to approve a drug's safety based solely on foreign data. Harvey Teff, *Drug Approval in England and the United States*, 33 AM. J. COMP. L. 567, 584 (1985).

248. Louis Lasagna, *Congress, The FDA, and New Drug Development: Before and After 1962*, 32 PERSP. BIOLOGY & MED. 322, 337 (1989).

249. *Id.*

250. Replication of efficacy and safety in human clinical trials requires the investigators to merely corroborate the conclusions already established by foreign studies. Therefore, pharmaceutical companies are barred from running creative experiments in order to discover novel information about the new drug. For example, the effects of different doses or dose intervals, the effects in different populations, the effects of interactions between drugs, and the effects of drug-disease interactions. The FDA's refusal to accept foreign clinical trials clearly inhibits innovation in drug research. Louis Lasagna, *On Reducing Waste in Foreign Clinical Trials and Postregulation Experience*, 40 CLINICAL PHARMACOLOGY & THERAPEUTICS 369, 369 (1986). On agreement between experts See generally Louis Lasagna, *Consensus Among Experts: The Unholy Grail*, Summer PERSP. BIOLOGY & MED. 537 (1976).

251. Louis Lasagna, *On Reducing Waste in Foreign Clinical Trials and Postregulation Experience*, 40 CLINICAL PHARMACOLOGY & THERAPEUTICS 369, 369 (1986).

trials,<sup>252</sup> unease about validating foreign data,<sup>253</sup> perceived poor design of foreign experiments,<sup>254</sup> and an extraordinarily high level<sup>255</sup> of statistical problems.<sup>256</sup> These safety barriers remain unchanged by the 1991 Reforms. It is unlikely that a simple statement, issued without substantiation, will bring the FDA to disregard their concerns about the safety of data produced abroad.

Reciprocity among nations in approving new drugs would certainly reduce the time and expense involved in approving new drugs, but variations traditionally and naturally occurring between United States and foreign research standards make reciprocity unlikely. These problems include the facts that: foreign protocols are traditionally less detailed than American protocols in terms of judgment and measurement of efficacy;<sup>257</sup> foreign research investigators are unaccustomed to being closely monitored through recorded data;<sup>258</sup> foreign researchers credited with impressive publications and academic credentials are often least responsive to discipline from their sponsors;<sup>259</sup> human interpretation of statistical norms and computer programs differ across cultures;<sup>260</sup> foreign companies have difficulty accepting FDA standards as truly necessary;<sup>261</sup> and the trial report document in other countries contains less data than in the United States.<sup>262</sup> All of these shortcomings of foreign research cause the FDA to be concerned about the safety of a foreign approved drug for the United States market.

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252. *Id.* at 370. Rejection of Europe's medical research standards lies directly in conflict with the FDA's idealistic proposal that it identify two or three key countries the FDA believes to have safety and efficacy standards in line with the FDA's own. Recommendations, *supra* note 13, at 43,623.

253. The FDA maintains that it has no way of knowing what was discarded from the foreign data base. Louis Lasagna, *On Reducing Waste in Foreign Clinical Trials and Postregulation Experience*, 40 CLINICAL PHARMACOLOGY & THERAPEUTICS 369, 370 (1986).

254. *Id.*

255. These problems include high drop-out rates, ill-defined criteria of effectiveness, and lack of knowledge of what was discarded from the data base. *Id.*

256. *Id.*

257. Foreign methods for testing are usually less detailed in reporting what laboratory tests are to be performed than similar American tests. Also, foreign protocols traditionally fail to detail variables such as criteria for judging efficacy. *Id.*

258. In particular, European testing seldom audits report forms against raw data in the physician's office. *Id.*

259. *Id.*

260. For example, patients who are dropped from the study may include patients who begin the study and then fail to complete the study. *Id.*

261. Foreign companies find it difficult to accept the need for the full plethora of statistical analysis called for by the FDA in the United States. This analysis includes: an intent to treat analysis; a subgroup analysis of patients who meet most of the inclusive criteria; a group of subjects whose data are impeccable; and whatever additional analysis is required by the FDA statistician. *Id.*

262. *Id.*

United States pharmaceutical companies, realizing that they must abide by the FDA's attitudes, have responded by simply repeating every foreign study, whether the original studies were conducted by their own foreign subsidiaries or some other firm.<sup>263</sup> The 1991 Reforms fail to address these problems. Until foreign data meets FDA standards, the FDA will continue to reject foreign data as primary evidence toward the approval of new prescription drugs in the United States.

The recommendations by the President's Council on Competitiveness do not constitute reforms; they are merely a reiteration of current FDA policy.<sup>264</sup> Although foreign data will continue to be accepted as supplementary in the approval of new drugs, they will replace neither originally domestic investigations nor the FDA's demand for replication of foreign data in the United States. Regardless of the 1991 Reforms, foreign studies will not play the expanded role of primary evidence on which approval would be granted. All of the numerous barriers by which the FDA has historically justified its cautious rejection of foreign research data remain in place today. These barriers have not been eliminated by the 1991 Reforms.

The time delay between the discovery and the marketing of a new prescription drug, the costs of developing a new drug, and the processes to ensure safe and effective drugs, which have historically plagued the FDA, will continue with no abatement from the 1991 Reforms. If the FDA is to succeed at alleviating these problems, a different solution must be implemented.

## V. SOLUTION

A method by which the approval process for new prescription drugs could be sped up and costs lessened, while maintaining safety and efficacy standards, would include the following three steps: elimination of unnecessary animal and human studies,<sup>265</sup> limited initial marketing through approved hospital pharmacies,<sup>266</sup> and a mandatory reporting system of all drug interactions.<sup>267</sup> Other countries benefit from a post-marketing surveillance system of prescription drugs.<sup>268</sup> For example, Great Britain's drug approval system places greater emphasis on post-market surveillance rather than the more restrictive pre-

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263. *Id.*

264. Many of the measures adopted by the FDA in response to the 1991 Drug Approval Reforms were already being used in connection with AIDS drugs. *FDA Releases New So-So Rules for Drugs*, NATIONAL PUBLIC RADIO, April 9, 1992.

265. See *infra* notes 272-306 and accompanying text.

266. See *infra* part V.B.

267. See *infra* notes 307-331 and accompanying text.

268. WILLIAM M. WARDELL & LOUIS LASAGNA, *REGULATION AND DRUG DEVELOPMENT* 77 (1975).



marketing surveillance system used in the United States.<sup>269</sup> The difference in the approval rate of new prescription drugs is dramatic.<sup>270</sup> For example, between the years 1962 and 1971, Great Britain had nearly four times as many drugs exclusively available and twice as many years of prior availability of new drugs as the United States.<sup>271</sup>

#### A. Elimination of Unnecessary Studies

By the time a new drug has reached the required FDA stage of extensive testing in higher level animals<sup>272</sup> and humans, the drug is already known to be safe and effective.<sup>273</sup> These tests may take as long as seven years, cost tens of millions of dollars, and are primarily performed to determine side effects and dosage levels.<sup>274</sup> Yet, the FDA's prescription drug approval process places a high priority on lengthy and expensive animal testing as well as extensive clinical trials using human subjects prior to approval.<sup>275</sup>

Moreover, toxicity testing in animals can never guarantee a drug's safety in humans.<sup>276</sup> For example, thalidomide passed rigorous animal tests before being marketed abroad, showing no negative side effects in mice, rats, or hamsters.<sup>277</sup> Only after thalidomide was found to produce severe congenital birth defects in humans did retroactive testing find a single animal species that

269. The organization in Great Britain, which is concerned with the quality, safety, and effectiveness of new drugs, is the Committee on the Safety of Medicines (CSM). After a new drug is approved for marketing, the CSM conducts postmarketing surveillance through a card system. When a patient reports an adverse effect from a drug to a doctor, the doctor fills out a card and mails it to the CSM. This enables the CSM to identify patterns of adverse reactions and take the appropriate action. John P. Dillman, Note, *Prescription Drug Approval and Terminal Diseases: Desperate Times Require Desperate Measures*, 44 VAND. L. REV. 925, 932-33 (1991).

270. *Id.*

271. WILLIAM M. WARDELL & LOUIS LASAGNA, REGULATION AND DRUG DEVELOPMENT 77 (1975).

272. These include animals such as dogs and primates. *Id.*

273. *Id.* at 137-39.

274. *Id.*

275. See generally Louis Lasagna, *Congress, The FDA, and New Drug Development: Before and After 1962*, 32 PERSP. BIOLOGY & MED. 322 (1989).

276. Max Sherman & Steven Strauss, *Thalidomide: A Twenty-Five Year Perspective*, 41 FOOD DRUG COSM. L.J. 458, 464 (1986). European countries, such as Great Britain, demand only six-month animal studies in two separate species whereas the United States requires the same tests to be at least twelve months in length.

A. Alister Dunning, *Regulation, New Drug Development, and the Question of Delay*, 41 FOOD DRUG COSM. L.J. 139, 139 (1986).

277. Max Sherman & Steven Strauss, *Thalidomide: A Twenty-Five Year Perspective*, 41 FOOD DRUG COSM. L.J. 458, 461 (1986).

paralleled the human teratogeny.<sup>278</sup> Suitable animal models are difficult to find<sup>279</sup> simply because other species do not share physiological attributes with human beings.<sup>280</sup>

Extensive pre-marketing animal testing may prove to be of little or no value, given both the limited ability to extrapolate from animals to humanity and the variations in the effects of drugs on different animals and species.<sup>281</sup> One study of six chemically dissimilar drugs that had been tested extensively in dogs, rats, and humans showed that animal testing failed to reveal more than fifty percent of the toxic side effects in human beings.<sup>282</sup> Studies also show that at least twenty percent of the positive predictions for toxicity and side effects in animals proved to be false in human beings.<sup>283</sup>

For example, Sir Alexander Fleming claimed that the penicillin project was successful although he never tested the drug on animals.<sup>284</sup> In fact, had animal tests been performed, penicillin would have never made it past the FDA's current approval process. Penicillin kills guinea pigs and is highly toxic to other laboratory animals, but remains one of the most useful and powerful drugs available.<sup>285</sup> One commentator has observed that the loss of even one drug such as penicillin due to excessively stringent animal testing requirements would harm more people than all of the drug toxicity in the history of modern drug development.<sup>286</sup>

There is no need to eliminate all animal testing. By instituting a tightly monitored system of post-marketing surveillance, animal testing requirements could be used without making them broader than necessary to protect the humans in the initial release of the prescription drug.

The present system of drug approval includes overly extensive and

278. Teratogeny is the production of abnormal organisms. WEBSTER'S THIRD NEW INTERNATIONAL DICTIONARY 2358 (1981).

279. "Of the numerous species of rabbits eventually tested for the effects of thalidomide on the fetus, only the New Zealand white rabbit was shown to be susceptible in the same way as the human fetus." Harvey Teff, *Drug Approval in England and the United States*, 33 AM. J. COMP. L. 567, 577 (1985).

280. Max Sherman & Steven Strauss, *Thalidomide: A Twenty-Five Year Perspective*, 41 Food Drug Cosm. L.J. 458, 464 (1986).

281. Harvey Teff, *Drug Approval in England and the United States*, 33 Am. J. Comp. L. 567, 577 (1985).

282. WILLIAM M. WARDELL & LOUIS LASAGNA, REGULATION AND DRUG DEVELOPMENT 138 (1975).

283. *Id.*

284. *Id.*

285. *Id.*

286. *Id.*

misguided clinical studies in human beings as well. Clinical trials in human beings occur in three phases. In Phase I studies, the drug is introduced into a small group of healthy human volunteers for a short period of time.<sup>287</sup> Phase I investigations primarily focus<sup>288</sup> on drug safety.<sup>289</sup> The FDA uses Phase I testing in order to prevent toxic compounds from reaching large groups of the population.<sup>290</sup> Later stages of testing in humans are used mainly to determine dosage, effectiveness, and side effects; information which could be more efficiently gathered under the proposed solution.<sup>291</sup>

Symptomatic patients are first administered a new drug in Phase II testing.<sup>292</sup> Phase II investigations monitor the drug's safety in a larger group of patients than Phase I testing.<sup>293</sup> Phase II testing also provides an opportunity for preliminary evaluations of efficacy.<sup>294</sup> However, these trials are still limited to small numbers of patients.<sup>295</sup> In fact, sponsors purposely limit Phase II trials to the smallest number of participants necessary to obtain scientifically valid results.<sup>296</sup>

Phase III testing is usually the final stage of human clinical testing.<sup>297</sup> By now the new drug is known to be a safe and effective treatment for a specific ailment.<sup>298</sup> In this phase the sponsor conducts at least two lengthy and time-consuming studies within a larger population, in an attempt to discover negative side effects within a representative population group. However, Phase III studies are usually limited to several hundred patients.<sup>299</sup> If the Phase III study is for a drug that is used to treat a novel disease, such as AIDS, thousands of patients who wish to participate will be turned away and forced to wait

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287. John P. Dillman, Note, *Prescription Drug Approval and Terminal Diseases: Desperate Times Require Desperate Measures*, 44 VAND. L. REV. 925, 928 (1991).

288. Other factors are also evaluated, such as rates of metabolism, absorption, and elimination. *Id.* at 928-29.

289. *Id.*

290. *Id.* at 929.

291. *Id.*

292. *Id.*

293. *Id.*

294. *Id.*

295. Scott H. Powers, Note, *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).

296. *Id.*

297. Occasionally the FDA will add a fourth testing phase which resembles post-marketing surveillance. During this phase, the FDA may re-evaluate approval and demand either a recall or relabeling. Because the FDA devotes little time to this phase, monitoring, relabeling, re-evaluation, or recalls are unlikely. John P. Dillman, Note, *Prescription Drug Approval and Terminal Diseases: Desperate Times Require Desperate Measures*, 44 VAND. L. REV. 925, 929 (1991).

298. *Id.*

299. *Id.*

several years for the study to be completed before they may seek to benefit from this new treatment.<sup>300</sup> In many cases, especially for patients waiting for life-saving drugs, this wait will be too long.

The FDA uses advanced animal and human studies to predict the toxicity and side effects of new drugs even though these tests have been proven to be of little use for these precise purposes.<sup>301</sup> Advanced clinical tests (Phase III) performed on humans add little information on the safety and efficiency of new drugs<sup>302</sup> and involve too small a population to adequately determine harmful side effects in those needing the drug.<sup>303</sup> Elimination of these unnecessary tests would cut years off the duration of new drug approval, thereby reducing costs and time delays, while maintaining strict levels of safety.<sup>304</sup> Moreover, the body of knowledge gathered would be significantly increased through mandatory reporting of the effects of a new drug after marketing the drug.<sup>305</sup> Because animal testing and clinical human trials prior to prescription drug approval, which are now utilized by the FDA, are of limited use<sup>306</sup> in projecting the drug's performance once it is marketed in real life situations, the number, length, and scope of such tests should be reduced, and replaced by more efficient and effective tests as proposed in the following sections.

#### *B. Limited Initial Release*

After a drug has passed the initial FDA standards for safety and efficacy, it will be made available through hospital pharmacies selected on the basis of physicians' participation in the mandatory reporting system. Initially releasing new drugs through pre-selected hospital pharmacies would make new drugs available to all persons interested in receiving innovative treatments under tight medical control. The population group undergoing testing, therefore, would increase substantially from the Phase III tests presently performed, and the security of such tests would not be compromised.

The drug will reach patients in need of its treatment more quickly, while not sacrificing the patients' safety. In fact, public safety will be enhanced because the drug and the patient will be closely monitored by the attending physician, the hospital, and the pharmacy dispensing the drug. Because new

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300. *Id.*

301. *See supra* notes 272-291 and accompanying text.

302. *See supra* notes 297-298 and accompanying text.

303. *See supra* notes 299-300 and accompanying text.

304. *See supra* note 274 and accompanying text.

305. *See infra* notes 307-331 and accompanying text.

306. WILLIAM M. WARDELL & LOUIS LASAGNA, REGULATION AND DRUG DEVELOPMENT 138 (1975).

drugs will only be dispensed through hospital pharmacies, there is more assurance that effects, both positive and negative, will be closely monitored. These effects will append the FDA's general body of knowledge through a system of mandatory reporting on all patients receiving new drug therapy.

### C. Mandatory Reporting

Closely monitored initial release of the prescription drug is better suited than the FDA's current system for discovering adverse side effects of drugs. Current Phase III clinical studies contain too small a sample to detect many side effects which occur infrequently.<sup>307</sup> Furthermore, current regulatory policies governing human research excludes pregnant women, particularly in the first trimester of gestation, as well as other sensitive population groups, from clinical trials.<sup>308</sup> Thus, another "thalidomide" could possibly be developed tomorrow, tested in animals without adverse reactions, shown to be highly efficacious in pre-marketing clinical trials,<sup>309</sup> and extensively marketed before it is known to harm fetuses.<sup>310</sup> Under current FDA policy, the only way to prevent another thalidomide tragedy is to forbid sensitive groups of the population from ingesting any new prescription drugs. Obviously this practice is impractical and unreasonable and must be replaced.<sup>311</sup> Under the proposed solution, even population groups sensitive to drugs would be tested and closely monitored thereby making new drugs available to them while closely protecting their safety and health.

Dr. William Wardell<sup>312</sup> points out that pre-marketing screening for safety and effectiveness is inevitably inadequate.<sup>313</sup> As it presently stands, the FDA's

307. *Id.* at 139.

308. *Id.*

309. Clinical trials (Phase III trials) are implemented after successful completion of initial safety and efficacy standards. This period of clinical trials is intended to assess, a drug's effectiveness and dosage range in treating a large number of human patients with a specific disease for which the drug is intended. These trials are the primary source of knowledge about a drug's toxic side effects in human beings. Max Sherman & Steven Strauss, *Thalidomide: A Twenty-Five Year Perspective*, 41 Food Drug Cosm. L.J. 458, 464 (1986).

310. *Id.* at 465.

311. *Id.*

312. Dr. Wardell of the Center for the Study of Drug Development, Departments of Pharmacology and Toxicity and of Medicine, University of Rochester Medical Center, is an expert in the field of drug regulation. He co-authored the book, *Regulation and Drug Development* with Dr. Louis Lasagna.

313. Dr. Wardell states:

Toxicity testing in animals can never guarantee a drug's safety in man; neither can the small numbers of closely monitored patients required for premarketing trials of efficacy guarantee its safety in the population at large. Given these facts, the actions of a regulatory agency should hinge to a large degree on the quality of postmarketing

method of prescription drug approval consists for the most part of only pre-marketing testing to prove a drug's safety and efficacy.<sup>314</sup> The pre-marketing screening approach has naturally led to the Agency's apprehension about approving new prescription drugs.<sup>315</sup>

The FDA's adoption of a unique post-marketing surveillance system that closely monitors a limited distribution of new prescription drugs through targeted and approved hospital pharmacies would eliminate the inadequacies of pre-marketing surveillance that continues to plague the United States drug approval process. A tightly controlled initial release of a new prescription drug could better inform doctors, pharmacists, pharmaceutical companies, and the FDA about the drug being released. The more informed the experts, the better protected the American public.

Whereas pre-marketing clinical studies investigate drug effectiveness and possible side effects within a small, non-representative population group, a system of post-marketing surveillance requires extensive feedback on the drug's performance among a more representative population. Testing on a more realistic population provides significantly more diverse as well as more inclusive data about the drug and its effects on the public.

The Joint Commission on Prescription Drug Use found that a post-marketing surveillance program would provide four major benefits: the

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surveillance. If postmarketing surveillance is poor or nonexistent, then the decision to approve a new drug is a grave and irreversible one; it should be delayed as long as possible (forever?) in the hope that exhaustive preclinical and clinical testing, together with the experience of other countries, will reveal all unsuspected toxicity in the drug before it is approved for marketing. If, on the other hand, postmarketing surveillance is rigorous enough to detect even rare drug toxicity promptly, then drugs could be introduced more rapidly, with confidence that . . . no widespread harm to the community will ensue even if the drug does turn out to induce unsuspected reactions.

William M. Wardell, *Therapeutic Implications of the Drug Lag*, 15 CLINICAL PHARMACOLOGY & THERAPEUTICS 73, 91 (1974).

314. See *supra* notes 287-297 and accompanying text.

315. As an FDA examiner explains:

Any time you approve a new drug, you're wide open for attack. If it turns out to be less effective than the original data showed, they can nail you for selling out to a drug company. If it turns out to be less safe than anybody expected, some congressman or a newspaper writer will get you. So, there's only one way to play it safe—turn down the application. Or at least stall for time and demand more research.

Louis Lasagna, *Congress, the FDA, and New Drug Development: Before and After 1962*, 32 PERSP. BIOLOGY & MED. 322, 335 (1989).

discovery of adverse effects unknown at the time of marketing,<sup>316</sup> quantification of the risks of known adverse effects,<sup>317</sup> quantification of drug efficacy,<sup>318</sup> and discovery of new indications.<sup>319</sup> This means that negative side effects can be limited while experience with a drug may also reveal a positive side effect providing a new use for the drug.<sup>320</sup> The most important advantage of a post-marketing monitoring system, however, is that it substantially increases physicians', pharmacists', manufacturers', researchers', and the FDA's knowledge base about new prescription drugs, thereby making drugs safer for their intended uses.<sup>321</sup>

Mandatory reports on the drug's performance and any side effects (positive or negative) would be regularly filed with the FDA under the proposed system. Increased knowledge about rare side effects that occur with a frequency of less than 1 in 10,000 would now be recorded and applied to all patients ingesting the new drug. Furthermore, because complete and detailed records will be kept for each patient receiving a new prescription drug, new developments and data can be quickly and effectively disseminated to the physicians and the patients who will directly benefit from such knowledge. This system of greater information feedback also protects the consumers because if harmful or dangerous effects are discovered, the FDA has an intact, established, and dependable network through which the drug can be rapidly and entirely removed from the public's hands.

Through the implementation of a thorough and carefully designed post-marketing surveillance system, consumers will receive safe and effective drugs years earlier than they would under the current system. Timely distribution of life-saving prescription drugs to patients will save American lives and improve

316. This includes the discovery of unknown adverse interactions between different drugs. Although many patients requiring prescription drugs are placed on more than one medication at a time, pre-marketing clinical tests specifically exclude this reality and instead investigate only the single drug's effects. Moving beyond the narrow confines of clinical human testing toward more comprehensive monitoring gives vitally important information about a drug's potential effect on the real population who will be using the drug.

317. This includes the evaluation of the moderation of adverse drug effects by various patient characteristics, concomitant drugs, and other factors. Pre-marketing trials are conducted with very few subjects, rarely exceeding 2000. Certain effects emerge only when the drug is used by large numbers of people. Audrey S. Rogers et al., *Physician Knowledge, Attitudes, and Behavior Related to Adverse Drug Events*, 148 ARCHIVES INTERNAL MED. 1596, 1596 (1988).

318. The efficacy information derived in human clinical trials requires supplementation after marketing with respect to the types of patients, the types of therapeutic practice, longer term efficacy, and efficacy in reference to new indications. New indications suggest a use for the drug in treatment of a disease for which it was not originally designed.

319. SENATE SUBCOMM. ON HEALTH AND SCIENTIFIC RESEARCH OF THE COMM. ON LABOR AND HUMAN RESOURCES, 96TH CONG., 2D SESS., FINAL REP. OF THE JOINT COMM'N ON PRESCRIPTION DRUG USE, INC. 27-28 (Comm. Print 1980).

320. *Id.*

321. *Id.*

American health. Consumers will also enjoy economic relief from the post-marketing surveillance system. Because pharmaceutical companies will receive a financial return on their investment much sooner, prescription drug prices should decrease, resulting in savings for the American consumer.

The FDA's present method of post-marketing feedback consists of a voluntary reporting system known as the Spontaneous Reporting System (SRS).<sup>322</sup> The United States suffers from a significantly lower rate of reporting adverse drug reactions as compared to other developed countries.<sup>323</sup> Although a recent study indicated that a high proportion of physicians detect adverse drug reactions in their patients, only five percent of such events were reported to the FDA.<sup>324</sup> In a recent survey of physicians' use of the FDA's SRS, nearly half of the 1,121 physician respondents were unaware that the FDA even had a system of adverse drug event reporting.<sup>325</sup> Further, only professional responsibility obligates a physician to report adverse patient experiences to the FDA.<sup>326</sup> Poor participation in the SRS could be cured by changing from a voluntary reporting system to a mandatory reporting system. Physicians would then be unable to prescribe the new drugs unless they assume the responsibility of reporting the results.

A commonly cited explanation for the physician's lack of reporting was the physician's hectic schedule, a factor that is unlikely to change soon.<sup>327</sup> Making the reporting of adverse drug events mandatory ensures that physicians participating in the post-marketing surveillance system allocate the time necessary to report such vital information to the FDA. Another reason the physicians gave for not reporting the negative event was that the physicians did not consider the event "serious."<sup>328</sup> A "serious" event is defined as an event that leads to or prolongs hospitalization, one which contributes to or causes death, or which is associated with cancer or a congenital anomaly.<sup>329</sup>

322. The FDA's SRS began in 1960. Stanley A. Edlavitch, *Adverse Drug Event Reporting*, 148 ARCHIVES INTERNAL MED. 1499, 1499 (1988).

323. Audrey S. Rogers et al., *Physician Knowledge, Attitudes, and Behavior Related to Reporting Adverse Drug Events*, 148 ARCHIVES INTERNAL MED. 1596, 1599 (1988). U.S. rates of reporting adverse drug reactions are, on the average, approximately twenty-five percent lower than those in Denmark, sixty percent lower than those in Canada, and fifty percent lower than those in the United Kingdom. Stanley A. Edlavitch, *Adverse Drug Event Reporting*, 148 ARCHIVES INTERNAL MED. 1499, 1499 (1988).

324. Stanley A. Edlavitch, *Adverse Drug Event Reporting*, 148 ARCHIVES INTERNAL MED. 1499, 1501 (1988).

325. Audrey S. Rogers et al., *Physician Knowledge, Attitudes, and Behavior Relating to Reporting Adverse Drug Events*, 148 ARCHIVES INTERNAL MED. 1596, 1599 (1988).

326. *Id.*

327. *Id.*

328. *Id.* at 1600.

329. *Id.*



Therefore, more subtle indications of an adverse effect are highly unlikely to be reported to the FDA in the present system.

A mandatory reporting system of drug effects, on the other hand, would facilitate significantly more information moving through established channels, including positive drug reactions. Currently, medical practitioners become aware of an adverse drug reaction only if the patient brings the complication to the physician's attention.<sup>330</sup> And, patients may be reluctant to report these reactions because they are often afraid to question their physicians.<sup>331</sup> The mandatory reporting system of post-marketing surveillance, however, would require doctors to inform their patients of the doctor's duty to report all drug side effects. This assures the patient that the physician will respect and act on patient reports, thereby increasing the incident of event reporting by patients to physicians.

#### D. Legal Authority

Some questions remain about the FDA's source of authority to institute these proposed measures. One possibility would be to amend the Food, Drug, and Cosmetic Act,<sup>332</sup> which has already been tried once.<sup>333</sup> The Senate passed the Drug Regulation Reform Act of 1979,<sup>334</sup> and although the bill ultimately failed to pass the House, it is nonetheless quite important. This bill signified a growing concern in Congress for the need to implement strong drug approval reform, uniting the concerns of legislators with such diverse views as Senators Kennedy, Javits, and Schweiker, all of whom were sponsors of the bill.<sup>335</sup>

The 1979 bill would have amended the Food, Drug, and Cosmetic Act (FDCA) by empowering the FDA to require post-marketing surveillance of a new drug at the time of the drug's approval,<sup>336</sup> with the rationale for the imposition of such to be given.<sup>337</sup> The proposed bill placed broad discretion in the FDA to require such post-marketing surveillance "at the time an application is approved . . . if [the FDA] determines that such a requirement is

330. Stanley A. Edlavitch, *Adverse Drug Event Reporting*, 148 ARCHIVES INTERNAL MED. 1499, 1501 (1988).

331. *Id.*

332. 21 U.S.C. §§ 301-394 (1988).

333. S. 1075, 96th Cong., 1st Sess. (1979).

334. *Id.*

335. Robert L. Fleshner, *Post-Marketing Surveillance of Prescription Drugs: Do We Need to Amend the FDCA?*, 18 HARV. J. ON LEGIS. 327, 339 (1981).

336. *Id.* at 340.

337. *Id.*

necessary or useful in evaluating the continuing safety of the drug.”<sup>338</sup> In addition, the FDA could require post-marketing surveillance, “if the FDA determines that such a requirement has become necessary and useful in evaluating the continuing safety of the drug.”<sup>339</sup> Although this bill was unsuccessful, it indicates congressional awareness of the need for and the benefits of a post-marketing surveillance.

A court has also shown a willingness to accept a post-marketing surveillance system by the FDA if that system is instituted due to the need for expert medical judgment in dealing with drug safety and efficacy.<sup>340</sup> The FDA tried a limited post-marketing surveillance scheme that was unsuccessful not inherently, but because of the scheme’s subject matter and the FDA’s rationale for instituting it. In *American Pharmaceutical Association v. Mathews*,<sup>341</sup> the FDA tried to institute a post-marketing surveillance system for methadone, a synthetic heroin.<sup>342</sup> The FDA attempted to introduce this surveillance not because of any untested state of the drug, but because of the drug’s addictive nature and the FDA’s perceived need to control access to it.

The FDA was prevented from instituting the post-marketing scheme.<sup>343</sup> The court reasoned that the FDA’s restrictions were designed to control drug misuse by persons who have no intent to try to use the drug for medical purposes rather than effectuating a system of assurance that the drug would be used with informed medical judgment about medical safety and effectiveness.<sup>344</sup> A post-marketing surveillance system, such as the one proposed here, instituted by the FDA for reasons of informed medical judgment about medicinal safety and effectiveness, would not incur the negative judicial scrutiny arising from the methadone incident.

The FDA may implement comprehensive post-marketing surveillance under the current statute.<sup>345</sup> Section 505(j)<sup>346</sup> of the FDCA would provide the

338. *Id.*

339. *Id.*

340. *American Pharmaceutical Ass’n v. Mathews*, 530 F.2d 1054 (D.C. Cir. 1976).

341. *Id.*

342. Methadone, an analgesic and antitussive agent, is a controlled substance and is used in the detoxification of heroin addicts. *TABER’S CYCLOPEDIA MEDICAL DICTIONARY* 887 (14th ed. 1981).

343. 530 F.2d 1054 (D.C. Cir. 1976).

344. *Id.*

345. Robert L. Fleisher, *Post-Marketing Surveillance of Prescription Drugs: Do We Need to Amend the FDCA?*, 18 *HARV. J. ON LEGIS.* 327, 336 (1981).

346. 21 U.S.C. § 355(j)(1) (1970) provides:

In the case of any drug for which an approval of an application filed pursuant to this section is in effect, the applicant shall establish and maintain such records, and make such reports to the Secretary, of data relating to clinical experience and other data or information, received or otherwise obtained by such applicant with respect to such

statutory basis for post-marketing regulations by the FDA.<sup>347</sup> Section 505(j) requires the applicant to maintain and establish records and make reports to the FDA when it is determined that certain information is necessary to facilitate a decision regarding whether approval of a new drug application should be withdrawn or suspended.<sup>348</sup> The Secretary<sup>349</sup> is allowed to withdraw approval of a New Drug Application if he determines that the drug may be unsafe.<sup>350</sup>

Under section 505(e) of the FDCA, the FDA already has the power to call for added studies in cases where the FDA finds that long-term studies may be "against the public interest."<sup>351</sup> When such a finding is made by the FDA, it "may approve the New Drug Application on condition that the necessary long-term studies will be conducted and the results recorded and reported in an organized fashion."<sup>352</sup> This is clearly a mechanism that would allow the FDA

drug, as the Secretary may by general regulation, or by order with respect to such application, prescribe on the basis of a finding that such records and reports are necessary in order to enable the Secretary to determine, or facilitate a determination, whether there is or may be ground for invoking subsection (e) of this section: *Provided, however,* That regulations and orders issued under this subsection and under subsection (i) of this section shall have due regard for the professional ethics of the medical profession and the interests of patients and shall provide, where the Secretary deems it to be appropriate, for the examination, upon request, by the persons to whom such regulations or orders are applicable, of similar information received or otherwise obtained by the Secretary.

347. 21 U.S.C. § 355(j)(1) (1970).

348. *Id.*

349. Reference is to the Secretary of the Department of Health and Human Services of which the FDA is a part.

350. 21 U.S.C. § 355(e) (1988) provides:

The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds (1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions for use upon the basis of which the application was approved. . . .

351. 21 C.F.R. § 310.303(a) (1992) provides in part:

A new drug may not be approved for marketing unless it has been shown to be safe and effective for its intended use(s). After approval, the applicant is required to establish and maintain records and make reports related to clinical experience or other data or information necessary to make reports to make or facilitate a determination of whether there are or may be grounds under section 505(e) of the act for suspending or withdrawing approval of the application. Some drugs, because of the nature of the condition for which they are intended, must be used for long periods of time—even a lifetime. To acquire necessary data for determining the safety and effectiveness of long-term use of such drugs, extensive animal and clinical tests are required as a condition of approval. Nonetheless, the therapeutic or prophylactic usefulness of such drugs may make it inadvisable in the public interest to delay the availability of the drugs for widespread clinical use pending completion of such long-term studies.

352. *Id.*

to institute limited marketing of a new prescription drug pending long-term studies. This same mechanism, if applied more regularly to new prescription drugs, could lead to a system of post-marketing surveillance advocated here.

## VI. CONCLUSION

Due to unnecessary time delays, high costs, and inefficient mechanisms to determine safety, drug regulation in the United States is in need of reform. The United States consistently lags behind the rest of the developed world in the approval of new, innovative, and efficient medications. Other countries have benefitted from a post-marketing surveillance system of prescription drugs.<sup>353</sup> It is likely that the United States would benefit similarly. Drugs could be made available to the patients who are literally dying to get them, while reducing the costs of such drugs. Eliminating excessive animal and clinical human studies, which now add years to the approval process for new prescription drugs, could save time and money. The use of a system combining limited marketing release of a new drug with mandatory reporting of drug effects would guarantee an increase in the safety and efficacy of new prescription drugs, while shaving off years and millions of dollars from the process of new drug approval. The American public would greatly benefit from the adoption of this proposal by having access to innovative new medications sooner, being protected against a wide scope of harmful side effects, and being granted a reduction in costs of prescription drugs.

Mark A. Kassel

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353. Harvey Teff, *Drug Approval in England and the United States*, 33 AM. J. COMP. L. 567, 584 (1985).

