

# AIDS, EXPERIMENTAL DRUG APPROVAL, AND THE FDA NEW DRUG SCREENING PROCESS

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## INTRODUCTION

One of the most important statutory mandates that guides the Food and Drug Administration (FDA) serves to designate the agency as protector of the American people against commercial introduction of new drugs that are either unsafe or ineffective.<sup>1</sup> Over the past sixty years, this mandate has often placed the FDA at the center of controversy as a series of medication-induced calamities led to repeated episodes of public outrage and to tighter controls on pharmaceutical development.<sup>2</sup> Determinations with regard to the safety and efficacy of new drugs entail a highly technical regulatory process drawing on the esoterica of medicine, pharmacology, biostatistics, and clinical trial design.<sup>3</sup> Thus the FDA, in fulfilling its mandate, has historically served as a buffer against dangers that the public was unequipped to evaluate directly.<sup>4</sup> Ironically, the turn of the twenty-first century sees

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1. See Federal Food, Drug, & Cosmetic Act § 903, 21 U.S.C. § 393 (1995 & Supp. III 1998). See also U.S. FOOD AND DRUG ADMIN., FOOD AND DRUG ADMINISTRATION MODERNIZATION ACT OF 1997: FDA PLAN FOR STATUTORY COMPLIANCE 4-5 (1998) (discussing evolving nature of FDA's mission), available in <<http://www.fda.gov/oc/fdama/fdamapln/part1a.htm>>.

2. The most notable events were the elixir sulfanilamide tragedy of 1938 and the thalidomide disaster of the early 1960s. See *infra* notes 30-36 and accompanying text.

3. For background on the interdisciplinary and scientific aspects of the new drug review process, see generally *From Test Tube to Patient: New Drug Development in the United States*, FDA CONSUMER, NOV. 1987, at 4-15, continued in FDA CONSUMER, Dec. 1987-Jan. 1988, at 6-18, and FDA CONSUMER, Feb. 1988, at 8-14 [hereinafter *From Test Tube to Patient*].

4. There are two reasons why the public may be unequipped to evaluate the dangers of new drugs: first, because of the technical complexities that are involved; and second, because the necessary information is only produced subject to the regulatory standards imposed by the FDA.

a significant revision to the FDA's institutional role, once again in the wake of controversy. This time, however, the FDA has been criticized for overreaching its mandate and for unreasonably impeding access to new modes of treatment.<sup>5</sup> Reform efforts at the FDA have paralleled a shift in popular perception, such that the FDA, once widely regarded as a defender of the public welfare, is now more often portrayed as an albatross around the necks of pharmaceutical manufacturers and desperately ill patients.<sup>6</sup>

The emergence of the AIDS epidemic in the 1980s marked a seminal event in the evolution of new drug approval policy at the FDA. AIDS rapidly became known as a highly lethal infectious disease for which there were no conventional therapies. In consequence, those suffering from the disease were desperately in need of new forms of treatment, no matter how experimental or unorthodox. For a group of individuals facing imminent death from AIDS, the possibility that an experimental treatment could be unsafe or ineffective became largely irrelevant.<sup>7</sup> Perhaps unsurprisingly, the paternalistic and risk-averse procedures for FDA drug approval were widely viewed in the AIDS community as politically unresponsive and a death sentence for many persons with AIDS ("PWAs").<sup>8</sup> Whereas earlier drug-related public health crises had involved the FDA's response to unsafe drugs in the marketplace,<sup>9</sup> the AIDS epidemic placed the FDA in the unusual position of exacerbating a health care crisis by impeding the development of, and access to, new medications. Concerted political activism soon followed, and gradual liberalization of FDA drug development guidelines resulted from an increasing sentiment that risk-ben-

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5. See, e.g., *Revitalizing New Product Development From Clinical Trials Through FDA Review: Hearing on S. 1477 Before the Senate Comm. on Labor and Human Resources*, 104th Cong. 14-17 (1996) (statement of Senator Judd Gregg) [hereinafter Statement of Senator Judd Gregg].

6. See *id.*; see also *Revitalizing New Product Development From Clinical Trials Through FDA Review: Hearing on S. 1477 Before the Senate Comm. on Labor and Human Resources*, 104th Cong. 219-30 (1996) (statement of Fred W. Lyons, Jr., Chairman of Hoechst Marion Roussel, Inc., a multinational pharmaceutical manufacturer) [hereinafter Statement of Fred W. Lyons, Jr.].

7. For a background discussion on the emergence of the AIDS epidemic and the desperate struggle of patients seeking experimental treatments, see PETER S. ARNO & KARYN L. FEIDEN, *AGAINST THE ODDS: THE STORY OF AIDS DRUG DEVELOPMENT, POLITICS AND PROFITS* 1-70 (1992); NEAL ARTHUR DICKERSON, *PROTOCOL FOR A PLAGUE: AIDS RESEARCH, ACCESS TO LIFE-SAVING THERAPIES & DRUG APPROVAL* (1994); ARTHUR D. KAHN, *AIDS: THE WINTER WAR* 3-65 (1993).

8. See ARNO & FEIDEN, *supra* note 7, at 30-36. The term "PWAs," as used in this article includes not only persons with AIDS, but also those infected with the Human Immunodeficiency Virus (HIV).

9. See *infra* notes 30-36 and accompanying text for a discussion of the elixir sulfamidamide and thalidomide disasters.

efit decisions regarding new drugs might better be made by the patients whose lives depended on the drugs.<sup>10</sup>

New drug approvals in the United States exemplify a broader set of governmental regulatory decisions that occur at the threshold between law and science, and involve complex and multidisciplinary problem solving.<sup>11</sup> At the core of the regulatory process inevitably lurks a utilitarian calculus and an attempt to balance competing social interests.<sup>12</sup> On the one hand, new drug development holds out the promise of innovative treatments for debilitating disease, for extending the human life-span, and for relief of suffering. These are enormous potential benefits. On the other hand, the introduction of inadequately tested new drugs creates the risk of iatrogenic<sup>13</sup> injuries through toxic side effects, carcinogenicity, et cetera. Furthermore, the premature introduction of new drugs may create additional problems in the form of ambiguity surrounding the comparative efficacy of different treatments, or a reduction in the pool of individuals willing to participate as subjects in double-blind clinical trials.<sup>14</sup> Any regulatory regime designed to deal with new drug approvals necessarily invokes some balance between these risks and benefits.<sup>15</sup> Whether the FDA's regime has been "optimal" in the effort to strike a balance remains a subject of controversy.

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10. For a discussion on patients' fundamental life and liberty interests, see Bret L. Lansdale, *A Procedural Due Process Attack on FDA Regulations: Getting New Drugs to People with AIDS*, 18 HASTINGS CONST. L.Q. 417, 424-27 (1991); Stephen R. Salbu, *Regulation of Drug Treatments for HIV and AIDS: Contractarian Model of Access*, 11 YALE J. ON REG. 401, 423-28 (1994). For a more general argument in favor of informed consumer choice in risks for new pharmaceuticals, see Dale H. Gieringer, *Consumer Choice and FDA Drug Regulation* (1984) (unpublished Ph.D. dissertation, Stanford University) (on file with the Stanford University Library).

11. For a series of wide-ranging case studies on other examples of such regulatory decisions, see generally RISK VERSUS RISK: TRADEOFFS IN PROTECTING HEALTH AND THE ENVIRONMENT (John D. Graham & Jonathan Baert Wiener eds., 1995) [hereinafter RISK VERSUS RISK].

12. See John D. Graham & Jonathan Baert Wiener, *Confronting Risk Tradeoffs*, in RISK VERSUS RISK, *supra* note 11, at 1-41.

13. "Iatrogenic" refers to effects deriving from medical intervention, and in particular to ailments or disorders that result from medical treatment. See WEBSTER'S THIRD NEW INTERNATIONAL DICTIONARY OF THE ENGLISH LANGUAGE, UNABRIDGED 1119 (1986).

14. In other words, the public availability of untested new drugs might itself undermine the results of the research process, in the worst case by degrading the quality of information that emerges from clinical trials.

15. Even the alternative of complete deregulation in favor of laissez-faire capitalism involves a utilitarian calculus: namely, that social welfare is maximized in a world where no regulatory barriers exist to impede new drug development.

On a theoretical plane, several problems are manifest in the FDA's efforts to regulate new drugs, particularly in the context of AIDS. One such problem involves institutional paternalism. As alluded to earlier, the rationale for regulating new drugs is based partly on grounds that significant risks are involved in their introduction and partly on grounds that consumers (and perhaps even physicians) are poorly qualified to evaluate those risks in a vacuum. Thus, the FDA protects the public by forcing manufacturers to meet rigorous standards in demonstrating the safety and efficacy of new medications. A major drawback to this "protection" is the subordination of patients' autonomy interests to the impersonal judgment of an administrative agency.<sup>16</sup> Terminally ill patients lacking effective conventional treatments confront a risk-benefit determination very different from that of the general public. Such patients have far greater incentives than the larger public to gather their own information and to take risks. Consequently, to the extent that the FDA traditionally applied a single standard to examining new drug risks and benefits, the agency may have short-changed PWAs as compared to a more risk-averse general population. Revisions in FDA policy have made experimental drugs more rapidly available to patients with AIDS, placing greater decision-making power in patients' hands. The implications of this change are subtle and far-reaching.<sup>17</sup>

Another important policy issue in new drug development involves risk spreading. Clearly, many forms of federal regulation act to shift the burden of risks from one group of people to another.<sup>18</sup> Often such programs (e.g., Federal Aviation Administration inspections) serve to shift catastrophic risks away from small groups of people (e.g., airplane crash victims) by spreading associated costs across much larger groups of people (e.g., airline ticket purchasers). Similar effects arguably followed from the traditional FDA new drug approval policy. In one sense, this policy was very risk-averse, as it helped to prevent catastrophic safety risks from falling on small groups of consumers who comprised the market for particular new drugs. To the

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16. See Lansdale, *supra* note 10, at 426-27; Salbu, *supra* note 10, at 423-28.

17. For example, FDA policy reforms suggest that the scientific aspects of clinical trial design may be more flexible than previously understood. Nevertheless, proposals for wider application of FDA reforms to new treatments for non-life-threatening conditions are probably an exercise in limited utility. See Michael P. Peskoe, *Application of AIDS-Related Drug Approval Processes to Other Drug Therapies—A Different View*, 45 FOOD DRUG COSM. L.J. 357, 357-62 (1990).

18. See Graham & Wiener, *Confronting Risk Tradeoffs*, in RISK VERSUS RISK, *supra* note 12, at 10-19. See also STEPHEN BREYER, *BREAKING THE VICIOUS CIRCLE, TOWARD EFFECTIVE RISK REGULATION* 21-29 (1993).

extent that the costs of delayed development were distributed evenly across a much larger group of people, FDA procedures may have served to spread risks associated with a lengthy process.<sup>19</sup> AIDS, however, demonstrated a terrible flaw in the paradigm—the conservative drug approval policies at the FDA may have actually focused risks onto a population of terminally ill individuals by delaying approval of experimental treatments for the putative safety benefits of the larger public. Concerns about the risk-spreading or risk-focusing attributes of a regulatory regime go beyond the utilitarian calculus and raise questions in regard to fundamental values about when and how the government should get into the business of redistributing risk.<sup>20</sup>

An even more fundamental problem confronting regulators involves the prospect that some risks may simply be unamenable to quantitative evaluation. Environmental regulation in the face of global warming, for example, presents an enormous challenge—because there is no consensus in regard to models for climate change, there is no basis for formulating an “optimal” government response.<sup>21</sup> Similar difficulties apply to the FDA’s efforts to regulate new drug development. Neither the risks nor the benefits of a new drug can be known in advance of systematic efforts to assess them. Even then, the possibility remains for serendipitous undiscovered benefits (e.g., differential utility for particular patient populations or therapeutic uses beyond those under clinical trial), or calamitous undiscovered risks (e.g., obscure toxicities by interaction or long-term carcinogenicity). The premise that the FDA, through any hypothetical regulatory regime, could rigorously achieve an “optimal” balance of interests in the aggregate seems optimistic.<sup>22</sup> Even probabilistic estimates of risk depend on statistics that are vulnerable to the violation of underlying

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19. Note that risk spreading works in a manner analogous to commercial insurance—a large pool of people subsidizes the costs of research in order to prevent catastrophic injuries to a few.

20. Justice Breyer has suggested that costs may sometimes outweigh benefits in regulatory efforts to eradicate low-probability risks. See BREYER, *supra* note 18, at 10-19. Granting the truth of the proposition, it may nevertheless be desirable to spread such low-probability risks, particularly where the most likely victims are identifiable, *ex ante*, by means of a Bayesian calculus. It may be unethical for government to allow low-probability risk exposure when “low-probability” refers to the general population, but the exposure is confined to a much smaller and readily identifiable group of people.

21. See generally Jonathan Baert Wiener, *Protecting the Global Environment*, in RISK VERSUS RISK, *supra* note 11, at 193-225.

22. Note, however, that although the “optimal” regulatory solution may prove elusive, systematic evaluation of risk tradeoffs may nevertheless permit identification of risk-superior opportunities for reform. See Graham & Wiener, *Confronting Risk Tradeoffs*, in RISK VERSUS RISK, *supra* note 12, at 36-41.

assumptions—most notably the assumption that the future will resemble the past, *ceteris paribus*. Once again, political values come to the fore when an administrative agency struggles with decisions in a context in which risks are not only not defined, but may not even be estimable.

In this context, it should come as no surprise that the FDA's drug approval regime has been subject to considerable criticism in the decades since it was established in 1962,<sup>23</sup> and not solely at the hands of AIDS activists. Pharmaceutical manufacturers have long contended that FDA regulation has impeded the development of new drugs by generating long delays and by adding hundreds of millions of dollars to the development costs for every new drug ultimately brought to market.<sup>24</sup> Analysts outside the pharmaceutical industry have expressed concern that the costs of FDA drug approval are so high they will substantially discourage development for all but the most commercially promising new medications.<sup>25</sup> Some analysts have also asserted that FDA regulation has resulted in a "drug lag" in comparison with new pharmaceutical development in Western Europe.<sup>26</sup> Moreover, soaring prescription drug costs in America have been identified as a key factor in a related crisis over healthcare financing, and pharmaceutical manufacturers are quick to point the finger at the FDA as a major source of rising costs.<sup>27</sup>

The evolution of these assertions in the wake of the AIDS crisis reflects a coalescence of interest between AIDS activists and major

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23. The 1962 amendments established for the first time FDA pre-market approval responsibility for new drugs based on an empirical demonstration of their efficacy. See Note, *Drug Efficacy and the 1962 Drug Amendments*, 60 GEO. L.J. 185, 192-95 (1972) [hereinafter *Drug Efficacy*].

24. The time and expense associated with new drug development in the United States was estimated in 1990 to approach an average of twelve years and 230 million dollars per new drug. See *Drugs and Biologics: Hearings Before the Subcomm. on Oversight and Investigations of the House Comm. on Commerce*, 104th Cong. 1-2 (1995) (statement of Congressman Joe Barton) [hereinafter Statement of Congressman Joe Barton]. A more recent estimate in 1995 suggested an average development time of fifteen years and average costs in the range of 500 million dollars per new drug. See S. REP. NO. 105-43, at 6-7 (1997).

25. See Elizabeth C. Price, *Teaching the Elephant to Dance: Privatizing the FDA Review Process*, 51 FOOD AND DRUG L.J. 651, 656-57 (1996) (describing how FDA's "magnitude of risk aversion" has slowed approval of innovative products).

26. See *id.* at 657-59; see also Veronica Henry, *Problems with Pharmaceutical Regulation in the United States: Drug Lag and Orphan Drugs*, 14 J. LEGAL MED. 617, 637-38 (1993) (comparing United States' drug lag with that of Great Britain).

27. See *supra* notes 6 and 24. But see Mary T. Griffin, *AIDS Drugs & the Pharmaceutical Industry: A Need for Reform*, 17 AM. J.L. & MED. 363, 363 (1991) (discussing history of above-average profit levels among American pharmaceutical manufacturers, even in context of escalating research and development costs).

pharmaceutical companies, creating a political climate increasingly sympathetic to arguments for deregulation. In response to political and legislative pressures, the FDA has endeavored to accommodate the criticisms through a variety of new drug approval reform measures, including expanded access, parallel tracking, fast tracking or accelerated approval, treatment and "compassionate use" investigational drug exemptions, and the personal use import exemption.<sup>28</sup> Although these mandates have been targeted at divergent elements in the FDA's new drug approval regime, they possess the common aim of making new drugs, particularly new AIDS drugs, more rapidly and more widely available than new drugs would be otherwise. And, though the measures have led to considerable changes in new drug approval procedures since the 1980s, the FDA remains under considerable pressure to adopt further reforms, especially in the aftermath of the Food and Drug Administration Modernization Act of 1997 (FDAMA).<sup>29</sup>

The purpose of this paper is to examine the evolution of FDA new drug approval regulations in response to the AIDS crisis from the early 1980s to the present day. It will begin with a discussion of the new drug approval process as it developed prior to the emergence of the AIDS epidemic. Focus will then shift to the various FDA initiatives that were introduced in response to the AIDS epidemic and the manner in which those initiatives altered the balance of regulatory power and risk management in new drug approvals. Discussion will also concentrate on the policy implications of FDA procedures, and the responsiveness of FDA policy making to the political interests of AIDS activist groups. Finally, the paper will touch on the continuing reform efforts at the FDA in the wake of the legislative enactment of the FDAMA in 1997 and the future prospects for new drug development in the context of ongoing reform.

The institutional role of the FDA as protector of the American people through the rigorous screening of experimental new drugs has, in recent years, become subject to skepticism. Critics have frequently derogated the agency for its failure to consider the social costs of its procedures. Pharmaceutical companies would prefer a deregulated marketplace as a predicate to bringing new drugs more quickly to the public. AIDS activists have decried a paternalistic system that emphasizes agency judgment over individual choice and values controlled clinical trials over the reality of human suffering. The FDA's efforts in response to the criticisms reflect a genuine concern for the interests

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28. See *infra* notes 131-85 and accompanying text.

29. See Pub. L. No. 105-115, 111 Stat. 2296 (codified as amended in scattered sections of 21 U.S.C.).

of those suffering from fatal and untreatable illnesses. However, pressure for reform continues in this regulatory domain—a domain in which risk management may be hampered by risks not merely unknown, but also those not subject to probabilistic apprehension. This paper adopts the thesis that the FDA's commitment to maintaining rigorous clinical trial requirements is a necessary prerequisite to any meaningful evaluation of risks and benefits associated with experimental new drugs. Consequently, ongoing reform efforts should proceed with great caution.

## I

### THE FDA AND THE HISTORY OF NEW DRUG REGULATION

The history of federal regulation of new drug approvals in the United States dates back to 1938.<sup>30</sup> That year saw a major public health crisis in the distribution of elixir sulfanilamide, a solution which, notwithstanding its medicinal properties, also contained diethylene glycol, a poisonous solvent.<sup>31</sup> Dozens of fatalities resulted, and public outrage over the incident helped to build impetus for the passage of the Federal Food, Drug, and Cosmetic Act (FFDCA).<sup>32</sup> This legislation was noteworthy because it contained, for the first time, the statutory requirement that companies seeking to introduce new drugs to the marketplace first seek FDA approval by demonstrating drug safety for human consumption.<sup>33</sup> Whereas earlier efforts to regulate pharmaceutical manufacturers focused on the prevention of fraud, the FFDCA conferred on the FDA the power to set standards in safety testing and to prevent unsafe drugs from ever reaching the mar-

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30. See *Drug Efficacy*, *supra* note 23, at 186-91. Congress had earlier passed the Food and Drug Act of 1906, which made illegal the sale of adulterated or misbranded drugs, but did not regulate false claims of drug efficacy nor create any regulatory authority for pre-market review. See *id.* at 185-86. See also Lois K. Perrin, Note, *The Catch-22 for Persons with AIDS: To Have or Not to Have Easy Access to Experimental Therapies and Early Approval for New Drugs*, 69 S. CAL. L. REV. 105, 109 (1995).

31. Diethylene glycol was known to be poisonous in 1938, but the tragedy resulted from omission by the manufacturer of any empirical testing or literature review to establish drug safety. See Stephen J. Ceccoli, *The Politics of New Drug Approvals in the United States and Great Britain* 104 (1998) (unpublished Ph.D. dissertation, Washington University (St. Louis)) (on file with *New York University Journal of Legislation and Public Policy*). The manufacturer did, however, engage in testing of elixir sulfanilamide sufficient to insure that its taste and smell were appealing to consumers—arguably a demonstration of the chief concerns of a manufacturer in an unregulated market. See *id.*

32. See Ch. 675, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. §§ 301-392 (1994)).

33. See *Drug Efficacy*, *supra* note 23, at 186-87.

ket.<sup>34</sup> A major shift toward consumer protection through risk regulation had occurred.

An even more rigorous statutory mandate emerged from a second public health crisis that took place in the early 1960s. Thalidomide, a drug that was manufactured and distributed in Europe for treatment of pregnancy-related illnesses, was discovered to have teratogenic effects on human neonates.<sup>35</sup> Thousands of babies were born in Europe with terrible deformities as a result of the side effects of thalidomide, and the drug was rapidly yanked from the European markets.<sup>36</sup> Fortunately, thalidomide had not yet been approved for use in the United States, and thus a domestic crisis was averted. Nevertheless, a new wave of public outrage followed, and sentiment led, once again, to the passage of legislation. The 1962 amendments<sup>37</sup> to the FFDCA resulted in a number of changes to the existing FFDCA statute. Perhaps most importantly, the amendments served to expand the FDA's mandate in regard to the regulation of new drug approvals. Where previously the regulatory focus was limited to determining whether the new drugs were safe, the amended mandate added a requirement that new drugs also be examined to demonstrate their effectiveness.<sup>38</sup>

The 1962 amendments to the FFDCA ushered in a new era of necessitating affirmative FDA pre-market approvals for new drugs. Although the earlier 1938 legislation had created a framework in which manufacturers were required to submit new drug applications (NDAs) as a prerequisite to commercial development, regulatory approval of new drugs was not required under the original statute. Instead, absent agency disapproval of an NDA within sixty days of its submission to the agency, the NDA automatically became effective.<sup>39</sup> By contrast, the 1962 amendments made affirmative approval mandatory to the commercial distribution of new drugs, and further established requirements for the submission of empirical data supporting drug efficacy as a crucial element of the NDA process.<sup>40</sup> The post-1962 development of regulatory NDA guidelines under the statute involved a complex interplay between the promulgation of regulations and case law adjudication of contested issues. The historical

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34. See Ceccoli, *supra* note 31, at 104-05.

35. See *id.* at 107-09.

36. See *id.* See also ARNO & FEIDEN, *supra* note 7, at 30.

37. Pub. L. No. 87-781, 76 Stat. 780 (1962) (codified as amended in scattered sections of 21 U.S.C.).

38. See *Drug Efficacy*, *supra* note 23, at 192-93.

39. See *id.* at 188-89.

40. See *id.* at 192.

details of this evolution go beyond the scope of the current paper.<sup>41</sup> Most important for current purposes was the outcome of that process: an elaborate set of pre-market approval procedures that required extensive testing of new drugs for safety and efficacy, and established the controlled clinical trial as the empirical modality for meeting the efficacy standard.<sup>42</sup>

As set out by FDA regulations after the 1962 statutory amendments, the new drug screening process consists of several phases. The initial step involves the submission to the FDA of an “Investigational New Drug Application” (IND) to conduct drug research on human beings.<sup>43</sup> Submission of the IND includes available pre-clinical data on the toxicity and chemistry of the experimental drug.<sup>44</sup> Provided that the FDA does not reject the IND proposal, pharmaceutical researchers may then move on to Phase I testing. Phase I involves the first administration of the experimental drug to a small group of human volunteers.<sup>45</sup> The primary aim of Phase I trials is to gather pharmacology and toxicity information in regard to possible adverse drug effects on humans. Where such effects materialize, the experimental drug may be discarded if its therapeutic, or commercial, potential is unduly compromised. Presumably, this is the stage of testing at which obvious and substantially negative effects will be discovered—for example, those associated with diethylene glycol poisoning.<sup>46</sup>

Assuming that the results from Phase I testing are positive, pharmaceutical researchers may then proceed to Phase II. The trials in Phase II typically involve small groups of subjects possessing whatever condition the experimental drug is designed to treat.<sup>47</sup> The

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41. For a cogent summary regarding the development of NDA regulations and case law in the decade after 1962, see *id.* at 195-222.

42. See 21 U.S.C. § 355(d) (1994) (setting efficacy standard for new drugs). See also 21 C.F.R. § 312.20-312.130 (1999) (promulgating regulatory provisions governing investigational process); U.S. FOOD AND DRUG ADMIN., GUIDANCE FOR INDUSTRY: PROVIDING CLINICAL EVIDENCE OF EFFECTIVENESS FOR HUMAN DRUG AND BIOLOGICAL PRODUCTS 1-4 (May 1998), available in <<http://www.fda.gov/cder/guidance/1397fnl.pdf>>.

43. See 21 C.F.R. § 312.20-312.38 (1999). Ordinarily, experimental drugs may not be employed on human subjects without prior FDA oversight through the IND procedure. See *id.* § 312.20(b).

44. See 21 C.F.R. § 312.23 (1999). See also U.S. FOOD AND DRUG ADMIN., GUIDANCE FOR INDUSTRY: CONTENT AND FORMAT OF INVESTIGATIONAL NEW DRUG APPLICATIONS (INDS) FOR PHASE I STUDIES OF DRUGS, INCLUDING WELL-CHARACTERIZED, THERAPEUTIC, BIOTECHNOLOGY-DERIVED PRODUCTS 4-15 (Nov. 1995), available in <<http://www.fda.gov/cder/guidance/clin2.pdf>>.

45. See 21 C.F.R. § 312.21 (1999).

46. See Ceccoli, *supra* note 31, at 104.

47. See 21 C.F.R. § 312.21.

drug can then be examined with regard to its effectiveness in ameliorating the target medical condition, as well as the relationship, if any, between drug dose and clinical improvement. Phase II trials also provide another opportunity to screen research subjects for adverse side effects in response to the drug. Phase II is the first stage of testing at which drug efficacy becomes a formal consideration; Phase II trials are conducted using a controlled, experimental methodology in order to determine such efficacy.<sup>48</sup> Although satisfactory results in Phase II are necessary to conduct subsequent trials in Phase III, the Phase II tests do not establish efficacy by themselves, even when the results are very promising.<sup>49</sup> The rationale for this policy derives from methodological concerns regarding the validity of small-scale studies of treatment outcome—such as are generally employed in Phase II. Nevertheless, this policy has been one of the more controversial aspects of the FDA's drug screening regime, as critics have long questioned the need for more rigorous evaluation of promising new drugs that emerge from Phase II—especially in regard to new drugs for otherwise untreatable terminal illnesses.<sup>50</sup>

Successful completion of Phase II prepares the way for the conduct of Phase III investigations on the new drug. Phase III studies are the sine qua non of the clinical trial process, at least as construed under the traditional FDA screening regime.<sup>51</sup> At this stage of the pre-approval process, hundreds or even thousands of research subjects are recruited to participate in large-scale, usually controlled trials of the experimental medication.<sup>52</sup> Phase III clinical outcome research serves to collect more extensive efficacy data than Phase II, closely focusing on the dose-response relationship for the new drug, as well as providing additional data regarding any potential for adverse effects or interactions. Successful completion of Phase III provides empirical evidence that the experimental drug is reasonably safe and effective in treating the target condition, and fulfills the manufacturer's research obligations under the statute and regulations.<sup>53</sup> Following the consummation of Phase III, the manufacturer may then submit to the FDA

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48. See *id.* See also *From Test Tube to Patient*, *supra* note 3, at 11.

49. See *From Test Tube to Patient*, *supra* note 3, at 12-13. However, one of the important "expedited approval" reforms has involved the accelerated review of some AIDS drugs, such as azidothymidine (AZT), after the completion of Phase II trials. See *infra* notes 103-05 and accompanying text.

50. See, e.g., NATIONAL CANCER INSTITUTE, FINAL REPORT OF THE NATIONAL COMMITTEE TO REVIEW CURRENT PROCEDURES FOR APPROVAL OF NEW DRUGS FOR CANCER AND AIDS 2 (1990).

51. See *From Test Tube to Patient*, *supra* note 3, at 12, 15.

52. See *id.* See also 21 C.F.R. § 312.21.

53. See 21 C.F.R. § 312.21.

all of the data generated in its research on the experimental drug in the form of a new drug application.<sup>54</sup> The FDA sometimes takes years in the review of submitted NDAs,<sup>55</sup> for which FDA approval is the final step that leads to sales of the new drug in the American marketplace.<sup>56</sup>

As may be apparent from the preceding description, the new drug screening process, as it developed following the 1962 amendment to the FFDCAs, is both laborious and expensive for prospective pharmaceutical manufacturers. Less obvious, however, may be the full extent of the barriers thereby imposed to development. Estimates in the 1970s indicated that the process of introducing a new drug to the market, beginning with the initial bench research in the laboratory and ending with FDA approval of the new drug application, took on average eight years to complete and incurred costs in excess of fifty million dollars per drug.<sup>57</sup> These delays and costs only increased over time, and arguably led to a drug lag between the United States and Western Europe, where new drugs were far more readily available and controls on development were much more limited and more market-based.<sup>58</sup> Critics castigated the FDA for creating disincentives to the development of new drugs at a time when technological innovation and consumer demand otherwise might have combined to generate more drug research and more new medications in the American market.<sup>59</sup> Some also noted that the costs of FDA regulation fell not solely on manufacturers, but also on patients with untreatable diseases for whom the commercial development of new drugs, given the existing barriers, was nonviable.<sup>60</sup>

Then too, even in the years before the AIDS epidemic, there existed desperately ill patients without hope for conventional treatment. Inevitably, conflicts arose regarding the application of restrictive FDA policies to untested drugs for untreatable conditions. Perhaps most

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54. See 21 C.F.R. § 314.50 (1999).

55. See Statement of Fred W. Lyons, Jr., *supra* note 6, at 224.

56. See *From Test Tube to Patient*, *supra* note 3, at 4.

57. See Statement of Fred W. Lyons, Jr., *supra* note 6, at 224-25.

58. In regard to escalating costs and delays associated with FDA review, see *supra* note 24. For a review of the literature on the putative drug lag between America and Europe, see Ceccoli, *supra* note 31, at 129-38. See also Henry, *supra* note 26, at 623-28.

59. See John Grossmann, *Greasing the Skids at the FDA*, HEALTH, Mar. 1983, at 28, 29. See also Ceccoli, *supra* note 31, at 130-32 (discussing criticism of FDA by Dr. William Wardell in 1970s).

60. The financial impediments to the development of new drugs with limited commercial potential became known as the "orphan drug" problem. See generally Henry, *supra* note 26, at 628-37. Congress responded with the Orphan Drug Act of 1983, which lengthened the intellectual property protection granted to orphan drugs, potentially increasing their profitability. See *id.* at 630.

notorious among this category was Laetrile, an untested and unapproved drug that, in the 1970s, was popularly believed to be an effective therapy for cancer. Notwithstanding such beliefs, the FDA steadfastly refused to approve Laetrile for distribution in the United States in the absence of any controlled trial data to suggest its efficacy.<sup>61</sup> Advocates, on the other hand, argued for access to Laetrile based on the personal autonomy interests of the terminally ill, particularly in the face of restrictive FDA approval procedures deriving from a conservative risk-benefit calculus.<sup>62</sup> Eventually, a group of terminally ill cancer patients brought suit against the FDA to enjoin its interference with the interstate trade in Laetrile.<sup>63</sup> In *United States v. Rutherford*,<sup>64</sup> the Supreme Court upheld the FDA's regulatory authority and rejected the premise of any exemption for the terminally ill to otherwise applicable safety and efficacy standards under the FFDCA.<sup>65</sup> In consequence, patients seeking access to Laetrile remained dependent on the black market or on treatment outside the country.<sup>66</sup> And, the FDA remained committed to rigorous empirical testing as a predicate to any approval for commercial distribution.<sup>67</sup>

In that vein, it is noteworthy to reiterate that the statutory language of the FFDCA required that pharmaceutical companies provide, as an element of their NDA filings, empirical evidence to demonstrate the efficacy of new medications.<sup>68</sup> Corresponding FDA regulatory provisions required that that evidence include at least one (and usually two) well-controlled (preferably "blind") trials showing statistically significant results for treatment of humans with the new drug.<sup>69</sup> This mandated empirical methodology has two very important elements: (1) a "controlled" trial, in which an experimental drug is compared to a placebo, or a known effective treatment in order to establish the comparative efficacy of the drug,<sup>70</sup> and (2) a "double-blind" trial,

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61. See PETER BARTON HUTT & RICHARD A. MERRILL, *FOOD AND DRUG LAW: CASES AND MATERIALS* 557-59 (2d ed. 1991).

62. See *id.* at 557-58.

63. See *id.* at 557.

64. See 442 U.S. 544 (1979).

65. See *id.* at 554-59.

66. For a summary of the litigation over Laetrile, see generally Kathryn A. Piffat, *Liability for Injuries Caused by Unapproved Pharmaceuticals Marketed to U.S. Consumers Abroad*, 7 B.U. INT'L L.J. 155, 167-71 (1989).

67. See *id.*

68. See 21 U.S.C. § 355(d) (1994).

69. See 21 C.F.R. § 314.126 (1999).

70. Current regulations recognize several different empirical methods as forms of control. See *id.* These include dose-comparison, historical comparison, and active treatment, as well as placebo. See *id.*

which involves random assignment of research subjects to the experimental and control groups, under conditions in which neither the doctors nor the research subjects know who is getting the experimental drug and who the control.<sup>71</sup> The history of experimental medicine and research psychology had demonstrated that uncontrolled, unblinded clinical trials were systematically vulnerable to experimenter bias, placebo effects, and the like.<sup>72</sup> For that reason, the double-blind trial became the “gold standard” for clinical outcome research regarding new forms of treatment.

It was in this regulatory context that the AIDS epidemic emerged in the 1980s. FDA procedures in the preceding twenty years had mostly evolved along the lines of protecting the public from dangerous and ineffective drugs through pre-approval standards based on what the FDA construed as rigorous science. Despite the mounting criticisms of pharmaceutical companies and terminally ill cancer patients, the FDA remained, to outside appearances, mostly unconcerned with the costs incurred by its drug approval regime, especially in terms of the administrative disincentives and barriers raised to the development of desperately needed new forms of treatment. It took the AIDS epidemic, and the social activism that accompanied it, to fracture the traditional paradigm.<sup>73</sup> The next section of this paper will briefly survey the emergence of the epidemic and concomitant political activism, examining its role in fostering change in FDA policy.

## II

### AIDS, ACTIVISM, AND PRESSURE FOR CHANGE

Acquired Immune Deficiency Syndrome (AIDS) was first identified in the United States in the early 1980s, as disproportionate numbers of homosexual men began to fall victim to obscure but deadly forms of illness.<sup>74</sup> In a short span of time, it became known that these disparate illnesses were somehow linked, and further that vulnerability to the underlying condition was not limited to homosexual men but had also begun to appear in other groups of people—hemophiliacs and intravenous drug users.<sup>75</sup> AIDS was designated as such by the Cen-

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71. *See id.*

72. For background on the double-blind methodology and the ubiquity of placebo effects, see generally Seymour Fisher & Roger P. Greenberg, *The Curse of the Placebo: Fanciful Pursuit of a Pure Biological Therapy*, in *FROM PLACEBO TO PANACEA: PUTTING PSYCHIATRIC DRUGS TO THE TEST* (Seymour Fisher & Roger P. Greenberg eds., 1997).

73. *See infra* notes 97-102 and accompanying text.

74. *See ARNO & FEIDEN, supra* note 7, at 2-4.

75. *See id.* at 4.

ters for Disease Control (CDC) in 1982.<sup>76</sup> Unfortunately, subsequent progress in understanding the new disease was relatively slow. By 1983, American and French researchers had made substantial strides toward isolating the viral pathogen that causes AIDS (dubbed the Human Immunodeficiency Virus or HIV).<sup>77</sup> Nevertheless, the development and approval of treatments for AIDS remained years away, and response to the disease by public health authorities was viewed by many, particularly in the gay community, as unconscionably slow.<sup>78</sup> In the absence of empirically validated effective treatment, AIDS and the opportunistic infections that accompanied it rapidly became known as a death sentence for its victims.

AIDS is a disease of the human immune system in which a retroviral infectious agent hijacks the body's own natural protective mechanisms and thereby destroys the very physiological defenses that might otherwise operate to combat the illness.<sup>79</sup> The term "AIDS" more precisely refers to the symptomatic phase of HIV infection, a condition characterized by substantially compromised immune function and often by secondary, opportunistic diseases that exploit the vulnerability of a weakened immune system.<sup>80</sup> Prior to the manifestation of full-blown AIDS, infection with HIV frequently involves a prolonged and asymptomatic latency period.<sup>81</sup> The latency period contributes to the passage of the virus, as its victims may transmit the virus while remaining entirely unaware of its presence. Transmission of the virus occurs through the sharing of infected body fluids, as through blood transfusion or sexual intercourse.<sup>82</sup> As a result, the virus poses the greatest threat of infection to those who are most frequently exposed to the body fluids of large numbers of other persons. Consequently, AIDS propagated very successfully in the early years

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76. *See id.*

77. *See id.* at 12-14.

78. *See id.* at 4-7. *See also* James J. Eigo, *Expedited Drug Approval Procedures: Perspective from an AIDS Activist*, 45 *FOOD DRUG COSM. L.J.* 377, 378 (1990).

79. *See* ARNO & FEIDEN, *supra* note 7, at 15-17. *See also* NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES, NIAID FACT SHEET: HIV INFECTION AND AIDS (1997), available in <[http://www.aegis.com/pubs/niaid\\_fact\\_sheets/1997/niaid97\\_fact\\_sheet\\_hivinf.html](http://www.aegis.com/pubs/niaid_fact_sheets/1997/niaid97_fact_sheet_hivinf.html)>.

80. *See* NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES, *supra* note 79.

81. *See id.*

82. *See id.*

among the segments of the male homosexual community in which promiscuous sexual contacts were commonplace.<sup>83</sup>

One of the most noteworthy features of the early years of the AIDS epidemic was the manifestation of the disease primarily in politically unpopular minority groups. Initially, AIDS was widely recognized as a "gay disease," a public misapprehension that required years to correct.<sup>84</sup> Other groups that first appeared vulnerable to the disease, such as intravenous drug users, were similarly unpopular and outside of the political mainstream.<sup>85</sup> To the extent that society responded to the epidemic in these groups, it did so with a significant degree of moral disapprobation.<sup>86</sup> Some religious conservatives even suggested that the disease was a punishment for the immoral behavior of its victims.<sup>87</sup> Such judgments subsequently became less palatable, as AIDS began to spread to the wider population.<sup>88</sup> Nevertheless, social responses to AIDS were frequently grounded in fear and superstition as the public became concerned about the possibility of transmission through casual contact.<sup>89</sup> Meanwhile, the official public health response to the AIDS epidemic was tepid. Despite the absence of effective treatment and the looming prospect of a major public health crisis, AIDS remained a low-profile political issue through 1987.<sup>90</sup> During this time, government research expenditures on AIDS were very limited, and the FDA had yet to approve any treatments.<sup>91</sup> It was in this political context that a militant AIDS activist movement was born.

AIDS activism in the gay community began with a growing perception that the government response to the epidemic was inadequate. From the early days of 1982 and 1983, persons with AIDS confronted

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83. See ARNO & FEIDEN, *supra* note 7, at 2-3 (describing how politics of gay liberation that began in 1970s led to free and frequent sexual activity among large numbers of gay men).

84. See *generally id.* at 4-5 (noting that in initial stages of epidemic, disease was identified by rare opportunistic infections in small groups of gay men and was referred to as "Gay Related Immune Deficiency").

85. See Eigo, *supra* note 78, at 378.

86. See, e.g., ARNO & FEIDEN, *supra* note 7, at 4-5.

87. See KAHN, *supra* note 7, at 3. One anecdotal report even attributed such sentiments to an FDA investigator, based on statements he allegedly made in 1990. See ELAINE FEUER, INNOCENT CASUALTIES: THE FDA'S WAR AGAINST HUMANITY xiii-xv (1996).

88. Revelations of HIV-positive status by celebrities such as Rock Hudson and Magic Johnson brought the epidemic into sharp focus for many non-homosexuals. See ARNO & FEIDEN, *supra* note 7, at 10. So too did the story of Kimberly Bergalis, a young heterosexual woman who was infected with HIV by her dentist. See *id.* at 10-12.

89. See SUSAN SONTAG, AIDS AND ITS METAPHORS 25-27 (1989).

90. See Eigo, *supra* note 78, at 378-79.

91. See KAHN, *supra* note 7, at 3-5.

the abyss of a lethal illness for which no effective treatment existed. Not surprisingly, PWAs rediscovered an axiomatic truth: For those otherwise facing the prospect of imminent death, any avenue of hope, no matter how unconventional or improbable, becomes a necessary object of pursuit. With no experimental drugs available through the government research pipeline, PWAs began to turn instead to untested compounds for which there were anecdotes or rumors in support of efficacy in treatment.<sup>92</sup> Such anecdotes and rumors abounded, and many PWAs rushed into self-treatment with untested and unapproved remedies such as AL-721, an egg yolk lipid derivative, and dextran sulfate, as well as other, more obscure forms of treatment.<sup>93</sup> Furthermore, in the absence of commercially available treatments, some PWAs began to synthesize their own “medicines” using kitchen chemistry with sometimes disastrous results.<sup>94</sup> Black market buying clubs arose to facilitate the purchase of drugs that were unapproved (hence illegal) in the United States, but which were available on the open market overseas.<sup>95</sup> And, all of this occurred in an environment where good information about the effectiveness of treatments was unavailable because the treatments had emerged entirely outside the regulatory purview of the FDA. Initial desperate enthusiasm for the newest treatment fad would die down as evidence accumulated to suggest its inefficaciousness.<sup>96</sup>

A broad spectrum of AIDS activist organizations coalesced in response to the disparate needs of the AIDS community, and to fill in the gaps in then inadequate government support services. For example, Gay Men’s Health Crisis (GMHC), one of the oldest AIDS activist organizations, was founded in 1981 in New York in order to provide AIDS-related health education and counseling for PWAs, as well as to lobby for improved government services related to AIDS.<sup>97</sup> The People With AIDS Health Group, also a New York organization, was formed as a black market buying club in 1987 and was designed to facilitate access for patients and their doctors to untested and unap-

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92. See, e.g., ARNO & FEIDEN, *supra* note 7, at 61-70.

93. Several such treatments, including dextran sulfate, isoprinosine, and ribavirin, were initially promising chemical compounds available through the black market and were later discredited as ineffective in treating AIDS. See *id.* at 61-65, 71-82, 209. See also KAHN, *supra* note 7, at 14-19.

94. This was reportedly a particular problem with AL-721. See ARNO & FEIDEN, *supra* note 7, at 65.

95. See *id.* at 60-70.

96. See *id.*

97. See *At a Glance: Departments and Mission*, GAY MEN’S HEALTH CRISIS (visited Mar. 24, 2000) <<http://www.gmhc.org/aboutus/gmhcmain.html>>.

proved experimental AIDS treatments.<sup>98</sup> A third AIDS organization, the AIDS Coalition to Unleash Power (ACT UP), was formed in 1987 as a militant activist group dedicated to achieving political and regulatory reform through confrontational tactics.<sup>99</sup> Although each of these groups emerged to address a different aspect of the AIDS crisis, the three were representative of a wider grass roots movement toward organization and activism within the AIDS community.<sup>100</sup> To the extent that the problems faced by PWAs had gone unaddressed by the government, activism offered PWAs themselves the opportunity to address some of the same problems. Activism and political organization were especially important with regard to the regulation of experimental drugs: an arena in which activists placed increasing pressure on the FDA, while they continued to promote access to new treatments through alternative, gray market channels.<sup>101</sup> The political pressure and public awareness fostered by AIDS activists were ultimately focal to later efforts to reform the FDA drug approval process.<sup>102</sup>

In the meantime, the FDA in 1985 approved the IND for an experimental new AIDS treatment called azidothymidine (AZT). AZT was noted to produce significant clinical improvement in patients during its Phase II trial, with findings of a substantial difference in six-month morbidity rates between patients in the placebo and drug groups of the study.<sup>103</sup> On this basis, AZT was rushed through the FDA approval process in record time and was introduced to the market by Burroughs Wellcome in 1987.<sup>104</sup> The two-year time frame from the FDA's initial approval of the IND to its later approval of the NDA was hailed as an enormous achievement and an example of what the agency could accomplish by prioritizing AIDS drugs for rapid review, as well as by early consultation with pharmaceutical developers

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98. See ARNO & FEIDEN, *supra* note 7, at 65-68.

99. See *id.* at 73-82.

100. These three organizations were by no means the only AIDS groups that formed in the 1980s. Many such organizations were founded across the country. Non-canonical listings of such organizations can be obtained at *HIV and AIDS Treatment and Prevention Information on the HIV InfoWeb*, HIV INFOWEB (visited Mar. 24, 2000) <<http://www.aegis.com/hivinfoweb/>> and HIV/AIDS Project, *Organizations and Projects*, VANDERBILT UNIV. MED. CTR. (last modified June 2, 1997) <<http://www.mc.vanderbilt.edu/resources/interests/aids/org.html>>.

101. See ARNO & FEIDEN, *supra* note 7, at 207-15 (discussing illicit Compound Q trials).

102. See Statement of Senator Judd Gregg, *supra* note 5, at 16 (citing needs of patients "with challenging medical conditions" in arguing for FDA reform).

103. See ARNO & FEIDEN, *supra* note 7, at 43.

104. See *id.* at 46-47.

in regard to the clinical trial process.<sup>105</sup> Another experimental AIDS drug, aerosolized pentamidine, was channeled through the FDA review process in a similarly rapid fashion between 1986 and 1989.<sup>106</sup> The pentamidine trial was noteworthy for its innovative use of a community-based research methodology, in which a group of San Francisco patients and their doctors were recruited into participation in the study.<sup>107</sup> The pentamidine and AZT approvals reflected a new degree of flexibility and urgency in the FDA's efforts to approve new AIDS treatments. The speed of FDA review for these drugs bore evidence to the pressure that the agency was under to produce new drug approvals and to find ways to do so quickly. Despite the successes of the AZT and pentamidine approvals, however, subsequent criticisms emerged from several directions.

After the approval of AZT, retrospective examination of the Phase II clinical trial led some reviewers to question the rigor of the experimental results.<sup>108</sup> Critics noted that only a small proportion of the research subjects actually completed the first six months of the trial, that the trial was "unblinded"<sup>109</sup> early, that inadequate toxicity and post-mortem data were collected, and that experimenter bias might have influenced the manner in which symptoms and drug side effects were recorded in the study.<sup>110</sup> Other reviewers noted that the study had been conducted on a homogeneous subject group comprised almost entirely of gay white males, thereby creating questions with regard to the efficacy of the drug in a more heterogeneous population of people suffering from AIDS.<sup>111</sup>

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105. See *id.* at 37-47; see also John A. Norris, *FDA's AIDS Program*, 12 NOVA L. REV. 1103, 1105-07 (1988).

106. See ARNO & FEIDEN, *supra* note 7, at 83-96 (discussing various forms of pentamidine). Aerosolized pentamidine is a treatment for pneumocystis carinii pneumonia (PCP), one of the opportunistic infections frequently associated with AIDS. See A. Bruce Montgomery, *How the Recent Changes in Expedited Drug Approval Procedures Affect the Work of a Clinical Investigator*, 45 FOOD DRUG COSM. L.J. 339, 339-40 (1990).

107. See Montgomery, *supra* note 106, at 340-41.

108. See KAHN, *supra* note 7, at 12. AZT was approved by the FDA shortly after its Phase II trial. See ARNO & FEIDEN, *supra* note 7, at 43. Phase III was bypassed because of the urgent need to get a treatment onto the market. See *id.*

109. When a study is "unblinded," all subjects receive the experimental drug, even those who formerly constituted the control group by virtue of their receiving only placebos. See KAHN, *supra* note 7, at 13.

110. See *id.* at 12-13. Perhaps unsurprisingly, the ex post criticisms of AZT were accompanied by the dawning recognition in the AIDS community that the drug was not a panacea for the illness: AZT was (and is) a very toxic medication that can, by itself, provide a significant but modest benefit in extending the lives of PWAs. See *id.* at 12-14. See also ARNO & FEIDEN, *supra* note 7, at 52-54.

111. See ARNO & FEIDEN, *supra* note 7, at 47.

Other methodological concerns were raised in the wake of the aerosolized pentamidine trials.<sup>112</sup> While many perceived the use of community-based testing as a leap forward in empirical methodology, one of the authors of the pentamidine trials expressed grave concerns about the difficulties inherent in maintaining a rigorously controlled trial while simultaneously responding to doctors' and patients' very valid concerns about individual health care.<sup>113</sup> In his analysis of the difficulties involved in the pentamidine trial, the author reached a pessimistic conclusion: "[U]ntil our society places greater value on the knowledge of whether a new therapeutic agent is safe and effective than [it does] on personal choice based on little or no information . . . research results will not meet the expectations of patients or society."<sup>114</sup>

The foregoing, in some sense, captures the fundamental dilemma at the heart of any effort to reform the new drug approval process, or to place increased decision-making power in the hands of PWAs. Efforts to expand drug access and to accelerate FDA review, unless very carefully designed, run the risk of degrading research results. Moreover, the information gathering function of clinical trial research is very different from the ordinary practice of medicine and may, at times, even be incompatible with it.<sup>115</sup> Controlled trials by definition involve patients and their doctors ceding some degree of control over treatment to clinical investigators. The prospect exists that strategic, self-interested research subjects might analyze the dose or composition of their experimental treatment, and on that basis modify or supplement treatment in order to optimize a personal assessment of welfare.<sup>116</sup> This sort of conduct might advance individual patients' autonomy interests, but it does so by undermining, to an unknown degree, the results from controlled research that is not truly under control. Detailed discussion of the policy implications of this dilemma will be deferred to a later section of this paper. For current purposes, it suffices to note that the history of experimental AIDS drug trials through the late 1980s casts the autonomy dilemma into sharp relief,

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112. See Montgomery, *supra* note 106, at 340-43.

113. See *id.* at 340-45.

114. *Id.* at 345.

115. I will act "for the benefit of my patients, and abstain from whatever is deleterious and mischievous." 14 ENCYCLOPEDIA AMERICANA 218 (1989) (Hippocratic Oath). This admonition becomes impossible to fulfill in an experimental context where investigator ignorance may lead to harm either from administration, or from denial, of a new treatment about which little is known.

116. At least one commentator has reported that a number of PWAs engaged in exactly this sort of conduct in the course of the AZT clinical trials. See ARNO & FEIDEN, *supra* note 7, at 51-52.

and this is the light in which the FDA's efforts to reform the drug approval process must be evaluated. The next section of this paper will examine a series of FDA reform measures adopted to facilitate the new drug approval process, and to make experimental, unapproved treatments more readily available to the patients most critically in need of them.

### III

#### THE FDA, NEW DRUGS, AND PROCEDURES FOR THE DESPERATELY ILL AND DYING

FDA regulation of new drug development since 1962 has involved an aggressive regime of pre-market review and mandatory approval prior to the introduction of new drugs into commerce.<sup>117</sup> As has been noted, the downside to the system is the substantial barrier that it imposes to new and innovative forms of treatment:<sup>118</sup> For those otherwise beyond the aid of modern medicine, the protection of FDA regulation offers scant comfort. Regulatory assessment of risks and benefits, as applied to the American population in the aggregate, may operate to the detriment of smaller groups of people whose risks and benefits differ dramatically from those of an idealized general public.<sup>119</sup> Nowhere is this more true than in the domain of an untreatable, terminal illness like AIDS. People confronting the prospect of imminent death face very limited risks from experimental medication, and even a small incremental probability for improvement may constitute an enormous benefit to them. The disjunction between the interests of the desperately ill and that of consumer protection for the broader public has long been recognized.<sup>120</sup> Over the span of many years, the FDA has undertaken a series of initiatives designed to bridge this gap, and to allow for wider access to unapproved treatments in the context of untreatable illnesses.

Prior to 1987, the FDA had long allowed for a compassionate use IND exemption to the otherwise strict prohibition against the employ-

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117. See *supra* notes 37-56 and accompanying text.

118. See Statement of Senator Judd Gregg, *supra* note 5, at 14-17.

119. For a discussion of subjectivity of values, uncertainty of knowledge, and diversity of individual circumstance, see Gieringer, *supra* note 10, at 5-6.

120. The disjunction is, in fact, the basis of the compassionate use exemption discussed *infra* notes 121-24 and accompanying text. Access to experimental drugs only becomes "compassionate" when denial of that access is manifestly injurious to the patient.

ment of unapproved drugs to treat severe forms of illness.<sup>121</sup> Such exemptions were granted on a case-by-case basis pursuant to the request of a patient's primary care physician and were dependent both on FDA approval and on the willingness of the pharmaceutical company to supply the experimental drug.<sup>122</sup> Although compassionate use INDs were oriented to the end of treatment rather than to the end of clinical research, critics nevertheless noted the inadequacy of compassionate use as an avenue for making experimental treatments more widely available to PWAs. In particular, availability of new drugs under compassionate use became a function of individual doctors' willingness and capacity to petition the FDA for its approval—a process that reportedly involved substantial paperwork, delay, and bureaucracy.<sup>123</sup> Even more important, compassionate use INDs were very dependent on the willingness of pharmaceutical companies to supply their experimental drugs, free of charge, based on the perceived potential for future profit under commercial development. Where the potential for future commercialization was limited or uncertain, the incentives for corporate collaboration with compassionate use INDs were undercut.<sup>124</sup> For these reasons, compassionate use INDs, insufficient to meet the increasing demands of large numbers of PWAs, failed to satisfy the humanitarian concerns which might have prompted the application of the procedure.

Another early regulatory effort designed to make unapproved treatments more available to desperate patients was the personal use import exemption.<sup>125</sup> Although manufacturers are generally proscribed from circumventing the FDA approval process by importation of unapproved drugs from overseas, the personal use exemption permitted individual citizens to import limited quantities of unapproved drugs for their own personal medical use.<sup>126</sup> In an apparent reversal

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121. See Perrin, *supra* note 30, at 119. See also Lisa Terrizzi, *The Need for Improved Access to Experimental Drug Therapy: AIDS Activists and Their Call for a Parallel Track Policy*, 4 ADMIN. L.J. 589, 600-01 n.62 (1991).

122. The compassionate use procedure was never formalized by the FDA through administrative rulemaking. See ARNO & FEIDEN, *supra* note 7, at 34-35.

123. Reportedly, the informality of the compassionate use procedure favored well-connected patients over those less fortunate. See *id.*

124. See Terrizzi, *supra* note 121, at 600-01 n.62.

125. See Audrey A. Hale, Note, *The FDA's Mail Import Policy: A Questionable Response to the AIDS Epidemic*, 16 RUTGERS COMPUTER & TECH. L.J. 169, 180-94 (1990). See also Eric Lindemann, Note, *Importing AIDS Drugs: Food and Drug Administration Policy and its Limitations*, 28 GEO. WASH. J. INT'L L. & ECON. 133, 134 n.8 (1994). As with the compassionate use procedure, the personal use exemption was never formally enacted into regulation. See *id.* at 134 n.8.

126. See Hale, *supra* note 125, at 180-81.

from the FDA's previous refusal to sanction the import of Laetrile, the personal use exemption offered PWAs much needed freedom in gaining access to treatment otherwise unavailable in the United States.<sup>127</sup> As alluded to earlier, buying clubs proliferated to facilitate the importation of experimental drugs from Europe and South America, a quasi-legal practice that occurred in the penumbra of the personal use exemption.<sup>128</sup> Once again, questions arose regarding possible drawbacks to the procedure. Availability of experimental drugs by import had the potential to sabotage American clinical trials, either by reducing the pool of voluntary research participants or by leading participants secretly to supplement their treatment, violating research protocols in hopes of avoiding the dreaded placebo. A more subtle issue involved the potential importation of drugs approved in the United States, but more cheaply available overseas—a financial disincentive to domestic pharmaceutical development.<sup>129</sup> Finally, to the extent that the personal use exemption allowed PWAs to opt out of the American regulatory scheme, it created exactly the situation that the scheme was designed to avoid: namely, the commercial exploitation of people desperately in need of treatment in the absence of information necessary to evaluate treatment utility.<sup>130</sup> Thus, although the personal use exemption served to increase the accessibility of unapproved drugs, it may also have exerted paradoxically negative effects on drug development and consumer choice.

Notwithstanding the mixed success of compassionate use INDs and the personal use import exemption, the propagation of the AIDS epidemic placed escalating pressure on the FDA to adopt new reforms in the drug approval process. By 1993, a more systematic series of reform measures had been undertaken, including regulations for expedited drug development (or “fast track”) and parallel track development. All of the measures were designed to accelerate the approval process and to make new drugs more rapidly and more widely available to PWAs. Each program will be discussed in detail below.

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127. *See id.* at 179-81.

128. *See* ARNO & FEIDEN, *supra* note 7, at 60-70.

129. *See* Lindemann, *supra* note 125, at 154-56.

130. This was very much the situation that occurred in the late 1980s with dextran sulfate, a widely imported, unapproved anti-AIDS drug that was later demonstrated to be ineffective as treatment. *See* ARNO & FEIDEN, *supra* note 7, at 71-82. One AIDS activist subsequently took the position that it was irrelevant whether the drug “worked,” and that PWAs should be allowed import access regardless. *See id.* at 81-82.

### A. Treatment IND and Expanded Access

Originally promulgated in 1987, the “Treatment IND” regulations serve to create a new protocol in the FDA drug approval regime, making experimental treatments available to PWAs on a pre-approval basis.<sup>131</sup> In contrast to the earlier compassionate use approach, treatment INDs are not primarily based on a case-by-case FDA review strategy. Instead, the approach involves identification of an experimental treatment with promising initial trial results, and allowing limited access to the treatment for desperately ill patients, while simultaneously gathering additional research data on treatment safety and effectiveness through the normal FDA regulatory scheme.<sup>132</sup> The treatment IND protocol becomes available to patients, physicians, and pharmaceutical manufacturers when the following four conditions are met: first, that the experimental drug is intended to treat a serious or immediately life-threatening disease; second, that no satisfactory treatment alternative exists to the experimental drug for purposes of a particular disease stage and clinical population; third, that the drug is already under investigation through controlled trials pursuant to an IND, or such investigation has already been completed; and fourth, that the sponsor of the IND is actively pursuing marketing approval for the new drug with due diligence.<sup>133</sup>

FDA regulations contemplate that pharmaceutical developers will take the initiative to submit a treatment IND application when appropriate, but the regulations also provide the FDA with the latitude to “deem” a treatment IND as submitted whenever the agency construes it to be appropriate.<sup>134</sup> Additionally, the regulations provide that licensed medical practitioners, with qualified patients, may apply for treatment IND access to an experimental drug in circumstances where the manufacturer has not already done so—a procedure reminiscent of the “compassionate use” exemption.<sup>135</sup>

Once a treatment IND protocol is authorized by the FDA, an experimental medication can then be obtained by patients who need it, prior to the approval of a corresponding new drug application and outside the context of formal clinical trials. Exactly when the new

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131. See Ellen C. Cooper, *Changes in Normal Drug Approval Process in Response to the AIDS Crisis*, 45 FOOD DRUG COSM. L.J. 329, 333 (1990) (comparing traditional methods of drug development and approval with new regulations for expedited FDA approval).

132. See *id.*

133. See 21 C.F.R. § 312.34 (1999); see also Cooper, *supra* note 131, at 333.

134. See 21 C.F.R. § 312.35 (1999).

135. See *id.*

drug becomes available for treatment, however, depends on FDA discretion and on the nature of the medical disorder at issue.<sup>136</sup> For “immediately life-threatening” conditions,<sup>137</sup> an experimental drug may be made available as early as during Phase II trials, provided that there is a reasonable basis to believe that the drug may be effective as treatment and further that it would not present unreasonable, significant risk of additional injury to patients.<sup>138</sup> For conditions classified as merely “serious,” an experimental drug may generally become available during Phase III testing, again provided that sufficient evidence of safety and effectiveness has been gathered.<sup>139</sup> The nature of the treatment IND procedure is to calibrate risks against benefits specifically for PWAs and other groups of seriously ill patients. At least in principle, where the marginal benefit from access to a new drug exceeds the risks associated with limited information, a treatment IND protocol serves to advance the medical interests of seriously ill patients. Thus, the introduction of treatment IND regulations represented an important shift in FDA policy by formally recognizing that consumer protection and stringent review of new drugs comprise only one side of the screening process.

Another important element of the treatment IND regulations is a provision that allows pharmaceutical companies to recover development costs by charging patients for access to experimental new drugs.<sup>140</sup> This system represents a departure from one of the central elements of the FDA’s traditional drug approval regime: its prohibition against commerce in drugs not approved.<sup>141</sup> An unfortunate consequence of the prohibition was to create disincentives to collaboration by pharmaceutical companies with compassionate use INDs. Given the extremely high costs associated with pharmaceutical development, companies possessed little commercial incentive to make experimental drugs available, free of charge, to large numbers of desperate patients. Moreover, ease of availability of experimental drugs outside the formal clinical trial process carried with it the possi-

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136. See 21 C.F.R. § 312.34.

137. See *id.* (defining immediately life-threatening as stage of disease “in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.”).

138. See *id.*

139. Note that “serious,” in contrast to “life-threatening,” is not defined under the regulation. The Commissioner of the FDA has significant leeway in evaluating the risks and benefits in considering treatment IND applications for experimental drugs to treat putatively “serious” diseases. See *id.*

140. See 21 C.F.R. § 312.7(d)(2) (1999).

141. See *Drug Efficacy*, *supra* note 23, at 192-95 (describing provisions of 1962 Act and noting that affirmative approval of drug was required).

bility of undermining that process and thereby impeding the progression of new drugs to the market.<sup>142</sup> The treatment IND regulations, by contrast, address the problem by allowing manufacturers to petition the FDA for authorization to charge for experimental drugs.<sup>143</sup> In so doing, the regulations draw a fine line between preventing the exploitation of PWAs and others suffering from life-threatening illnesses through commerce (and possible extortionate pricing) in untested pharmaceuticals, and at the same time encouraging manufacturers to supply experimental drugs on a pre-approval, but non-research basis. Not surprisingly, the wisdom and merits of this effort at balancing received a mixed reception, *ex post*, among members of the medical and AIDS activist communities.

Criticisms of the treatment IND concept have alleged conflicting deficiencies in the application of the regulations. One set of concerns focused on treatment INDs as a retreat from rigorous FDA safety standards with concomitant potential for financial exploitation of vulnerable PWAs.<sup>144</sup> Even in the absence of exploitation, treatment INDs raised the specter of iatrogenic harm to large numbers of patients who might receive experimental drugs early in the clinical testing process, and prior to any decent evaluation of drug effectiveness, toxicities, or invidious side effects.<sup>145</sup> A diametrically opposed concern, on the other hand, was the sense of many AIDS activists that treatment IND protocols did not go far enough in making experimental drugs available to people in need.<sup>146</sup> In particular, the regulations permitted the FDA substantial leeway in determining when, during IND trials, a

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142. In strategic terms, it is better for any individual patient to receive real experimental drugs through a compassionate use IND than to participate in a clinical trial in which one might receive a placebo. Consequently, a strategic pharmaceutical company would presumably be reluctant to give away experimental drugs, in effect helping to undermine the formal clinical trial process.

143. See 21 C.F.R. § 312.7(d)(2).

144. See ARNO & FEIDEN, *supra* note 7 at 97-109 (discussing FDA's initial response to AIDS epidemic and establishment of treatment INDs). Financial exploitation becomes a concern when patients may be charged high prices for a new drug based on very limited efficacy data—especially when administrative oversight might be compromised by the urgency of getting new drugs out quickly.

145. The treatment IND regulations are noteworthy for the absence of a formal efficacy threshold to establish when a new drug will qualify for the protocol; presumably, the FDA makes these determinations on a case-by-case basis. As to the possibility for iatrogenic injuries to patients, at least one experimental AIDS drug, suramin, led to drug-induced fatalities during its Phase II trial in the 1980s, and raised fears about the possible ill effects that might have followed had the drug been made widely available on a pre-approval basis. See *id.* at 98-99.

146. For example, activists criticized the first application of the treatment IND procedure in 1988 because access to the experimental drug trimetrexate was limited to patients who had had an adverse reaction to conventional treatments, and was denied

new drug might become available on a treatment IND basis. To the extent that treatment IND status is deferred until late in the clinical trials, availability of the new drug to needy patients is only mildly accelerated.<sup>147</sup> Additional concerns arose regarding access to high priced experimental drugs under treatment IND; drug costs represented another potential impediment to accessibility for PWAs without the resources to pay out of pocket and for whom insurance benefits would not cover the costs of experimental treatment.<sup>148</sup> Notwithstanding criticisms from both extremes, treatment IND protocols went forward as an FDA device to adjust the drug screening process in favor of the interests of PWAs and paved the way for additional regulatory reform measures including expedited access and parallel track development.

### B. Expedited Development and Accelerated Approval

Efforts to expedite FDA screening of new drugs comprise an institutional response to the general perception that the process of drug development, starting with pre-clinical lab work and ending with NDA approval, takes too long. Whereas expanded access initiatives such as treatment INDs seek to make experimental drugs available to patients prior to the submission of a new drug application, expedited review provisions instead focus on accelerating or short-cutting the ordinary clinical trial process in order to obtain full FDA approval in a shorter span of time.<sup>149</sup> A number of FDA innovations that were employed in the approval of AZT were subsequently codified into federal regulations in 1992 and 1993.<sup>150</sup> Respectively known as "Subpart E" and "Accelerated Approval" regulations, these reform measures introduced several new aspects of FDA review, including early consultation between the FDA and pharmaceutical developers, FDA monitoring of the clinical trial process, adoption of "surrogate

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to patients who simply failed to get better on conventional treatments. *See id.* at 101-02.

147. *See* Terrizzi, *supra* note 121, at 608-10 (critiquing effectiveness of treatment IND).

148. For background discussion on the problems of extending insurance coverage to experimental treatments, see Mary Ader, *Access to Investigational Treatments*, 6 HEALTH MATRIX 187 (1996).

149. *See generally* Sheila R. Shulman & Jeffrey S. Brown, *The Food and Drug Administration's Early Access and Fast-Track Approval Initiatives: How Have They Worked?* 50 FOOD AND DRUG L.J. 503, 511-17 (1995) (discussing FDA expedited review and approval reforms); *see also* Salbu, *supra* note 10, at 415-16.

150. *See* ARNO & FEIDEN, *supra* note 7, at 41-46 (discussing early and continued consultation during clinical trial process between FDA and manufacturer of AZT).

endpoints”<sup>151</sup> as standards for gauging treatment outcome, abbreviation of clinical trials prerequisite to NDA submission, and FDA authority to require Phase IV post-marketing research as a condition for NDA approval. Each of these measures will be discussed briefly below; together, they reflected a substantial shift in FDA policy to accommodate the reality of the AIDS epidemic and its attendant political pressures.

The expedited development regulations of Subpart E were initially proposed in 1988, shortly after the promulgation of the treatment IND procedure.<sup>152</sup> Codified in 1992, Subpart E established a series of measures to expedite FDA review of new drugs designed to treat life-threatening or seriously debilitating diseases.<sup>153</sup> At a policy level, the Subpart E regulations asserted the importance of flexibility in the FDA’s application of the statutory (FFDCA) standards of safety and effectiveness, particularly in recognition of the increased risk-tolerance of seriously ill patients for whom no satisfactory treatment alternatives existed.<sup>154</sup> Consideration of disease severity and lack of alternative treatments was specifically incorporated into the FDA’s risk-benefit determination in its approval of corresponding new drug applications.<sup>155</sup> More importantly, Subpart E established a collaborative framework in which early and repeated consultation between the FDA and pharmaceutical manufacturers served to facilitate clinical trials, and to insure *ex ante* that prospective research designs would meet with subsequent regulatory approval.<sup>156</sup> In addition, consultation between the FDA and manufacturers regarding expanded Phase II trials was established as a predicate to the elimination of Phase III trials in instances where sufficient safety and efficacy data was already gathered.<sup>157</sup> So-called “Phase IV” post-marketing trials were authorized as a device to postpone some of the research burden until after the approval of an experimental drug, again expediting access where ini-

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151. See *infra* notes 160-65 and accompanying text for additional discussion of surrogate endpoints.

152. See Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Procedures for Drugs Intended To Treat Life-Threatening and Severely Debilitating Illnesses, 53 Fed. Reg. 41,516, 41,523 (1998).

153. See 21 C.F.R. § 312.80 (1999). “Subpart E” refers to the designation of the expedited development regulations within Part 312 of Title 21 of the Code of Federal Regulations.

154. See *id.* (describing policy that animates Subpart E regulations).

155. See 21 C.F.R. § 312.84 (1999).

156. See 21 C.F.R. § 312.82 (1999) (discussing early consultation between FDA and manufacturers); 21 C.F.R. § 312.87 (1999) (regulating FDA monitoring of clinical trial process).

157. See 21 C.F.R. § 312.82.

tial clinical trial research yielded positive results.<sup>158</sup> Taken together, early consultation, consolidation of Phase II and Phase III clinical testing, and the possibility of post-approval testing served to radically alter the new drug approval process with regard to life-threatening illnesses, particularly for AIDS.

Accelerated approval regulations, made effective in 1993, went an additional step beyond Subpart E in modifying the traditional FDA review process.<sup>159</sup> The essential element of the accelerated approval regulations was the provision that “surrogate endpoints” could be employed as the empirical basis for FDA approval of a new drug.<sup>160</sup> In contrast to earlier clinical research practice relating to life-threatening disease, in which positive outcome was defined in terms of extended patient survival, the accelerated approval procedure established that outcome might instead be measured by intermediate physiological or biochemical effects where these were predictive of clinical benefit based on other empirical evidence.<sup>161</sup> Thus, for example, as subsequently applied to research on AIDS drugs, clinical trial outcome might be measured in terms of CD4 cell counts—an index of human immune function that marks the physiological progression of AIDS.<sup>162</sup> In fact, the accelerated approval regulations contemplate that surrogate endpoints may be employed in clinical trials even absent complete confidence in the connection between the ultimate benefit and the surrogate endpoint, provided that additional post-marketing studies are diligently pursued to validate the ultimate benefits of the new drug.<sup>163</sup> By allowing new drug approvals to proceed based on surrogate endpoint data, the clinical research process is potentially abbreviated by comparison with more conservative empirical methods.<sup>164</sup> The tradeoff, of course, lies in the prospect that some surrogate endpoints

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158. See 21 C.F.R. § 312.85 (1999) (discussing Phase IV post-marketing studies).

159. See 21 C.F.R. § 314.500 (1999) (providing for accelerated approval of drugs). See also 21 C.F.R. § 601.4 (1999) (providing for accelerated approval of biologicals, such as vaccines).

160. See 21 C.F.R. § 314.510 (1999).

161. See *id.*

162. See ARNO & FEIDEN, *supra* note 7, at 15-18; see also Shulman & Brown, *supra* note 149, at 515-17.

163. However, the FDA may attach conditions to an accelerated approval, including restricted distribution, advance review of advertising, and a streamlined procedure for removing the new drug from the market under a variety of circumstances. See Shulman & Brown, *supra* note 149, at 515.

164. One such conservative method is morbidity analysis. See *id.* at 514.

may turn out, *ex post*, to be less useful in predicting ultimate outcome than was apparent *ex ante*.<sup>165</sup>

Preliminary examinations of the impact of accelerated approval and Subpart E on the FDA drug review process suggest that the reforms truly have had the desired effect of reducing the development time for new drugs under these protocols. One empirical study found that the regulatory phase for drugs initially approved under Subpart E (and after the effective date of the regulations) was only 3.3 years—an enormous improvement over an estimated average of more than ten years of time to approval under the standard FDA review scheme.<sup>166</sup> On a similar note, data for AIDS drugs reviewed under expedited approval procedures indicated that FDA review time for such new drug applications averaged less than five months, substantially faster than the baseline approval time for NDA review, which has been estimated elsewhere to approach fifteen months.<sup>167</sup> Clearly then, the FDA's expedited development regulations reflect both a shift in FDA policy as well as a practical improvement in the speed with which the agency can bring new AIDS drugs (and drugs for other life-threatening conditions) to market. Questions about the appropriate use of surrogate endpoint data remain however, as does the fundamental dilemma involved in trading development time for increased risk in the new drug review process.<sup>168</sup> It also remains tautological that for people still desperate for access to new forms of treatment, even the accelerated version of FDA review is not fast enough.

### C. *Parallel Track*

Of the various federal initiatives designed to modify the FDA drug approval process, "Parallel Track" is the only such program exclusively targeted at AIDS and HIV-related conditions.<sup>169</sup> Deriving in

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165. In fact, this may have been the case with the use of CD4 cell counts as a surrogate marker in testing new AIDS drugs. *See id.* at 516-17.

166. *See id.* at 512-13. For a discussion of the baseline development time for new drugs under FDA review, see *supra* note 24.

167. *See Expanded Access and Expedited Approval of New Therapies Related to AIDS*, U.S. FOOD AND DRUG ADMIN. (last modified Mar. 5, 1998) <<http://www.fda.gov/oashi/aids/expanded.html>>. *See also* David A. Kessler, *Remarks by the Commissioner of Food and Drugs*, 52 FOOD AND DRUG L.J. 1, 1-2 (1997).

168. *See supra* note 145 and accompanying text regarding fears of the possibility of drug-induced injuries, or fatalities, as a function of expanded access to new drugs earlier in the clinical trial process.

169. *See Expanded Availability of Investigational New Drugs Through a Parallel Track Mechanism for People with AIDS and other HIV-Related Disease*, 57 Fed. Reg. 13,250 (1992) [hereinafter *Expanded Availability*]. *See also* Shulman & Brown, *supra* note 149, at 509-10.

spirit from earlier FDA and National Cancer Institute (NCI) experiences with providing access to unapproved cancer drugs outside of controlled clinical trials, the parallel track program was established in 1992 to facilitate treatment access to experimental AIDS drugs concurrent with the FDA's formal clinical screening process.<sup>170</sup> Although the parallel track program is conceptually similar to the treatment IND regulations that were codified several years earlier, the parallel track initiative went a step further: "Under this policy, expanded availability protocols might be approved for promising investigational drugs when the evidence for effectiveness is less than that generally required for a treatment IND."<sup>171</sup> The parallel track policy deliberately excluded diseases other than AIDS from its purview and, according to official comments, was intended as a pilot program to evaluate the incremental benefits and drawbacks of expanded access beyond that involved in the treatment IND or Group C procedures.<sup>172</sup> To date, the parallel track initiative has been far less frequently employed than the other FDA procedures for expanding access or expediting development, although this pattern may shift as new AIDS drugs continue to be synthesized.<sup>173</sup>

For practical purposes, the most important aspect of the parallel track policy is the evidentiary standard that it sets as a bar to the distribution of an experimental drug outside the clinical trial process;<sup>174</sup> to the extent that the standard is similar to that available under the treatment IND regulations, convergence between parallel track and treatment IND protocols seems likely.<sup>175</sup> Notwithstanding the policy statement that the parallel track procedure is intended to require a lower standard of safety and effectiveness than that employed under treatment IND, the policy guidelines invoke the ambiguity of a multi-factor balancing test in making parallel track determinations.<sup>176</sup> Some of the factors considered in the calculus are empirical information

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170. See Expanded Availability, *supra* note 169, at 13,250.

171. *Id.* at 13,256.

172. See *id.* at 13,256. "Group C" refers to a joint FDA-NCI protocol in which oncologists were permitted treatment access to experimental cancer drugs outside of controlled clinical trials. See *id.*

173. Only one new drug, stavudine, has been distributed under the parallel track protocol since the policy was formally published in 1992. See Shulman & Brown, *supra* note 149, at 510.

174. See *infra* notes 176-79 and accompanying text.

175. There is no formal effectiveness standard for determining when experimental drugs qualify for treatment IND status under FDA regulations. See *supra* note 145 and accompanying text.

176. See Expanded Availability, *supra* note 169, at 13,257 (establishing multi-factor balancing test).

showing promise of drug safety and effectiveness; preliminary laboratory data on pharmacokinetics, dose-response, and drug interactions; data sufficient to suggest an appropriate starting dose; description of the patient population designated to receive parallel track access; and assessment of the probable impact of parallel tracking on the recruitment of subjects for concurrent formal trials.<sup>177</sup> Exactly how this balancing test works in practice is unclear, although the policy guidelines do stipulate that FDA approval of Phase II testing and recruitment of Phase II research subjects is a prerequisite for expanded availability under parallel track.<sup>178</sup> The guidelines acknowledge public concerns about the possibility of delayed access due to the complexity of the balancing involved in parallel track determinations, but emphasize the need for such balancing as a predicate to flexible regulatory response to “the unique circumstances of particular drugs and patient populations.”<sup>179</sup>

Another important element of the parallel track policy is its invocation of a multi-agency regulatory process in order to move expanded access decisions outside the exclusive jurisdiction of the FDA. In particular, the policy contemplates that applications for parallel track status will be reviewed by the AIDS Research Advisory Committee (ARAC), an expert consultative panel chartered by the National Institute for Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH).<sup>180</sup> The ARAC reportedly consists of expert physicians, non-government scientists, PWAs and representatives of AIDS activist organizations who together serve to review parallel track applications and to make recommendations regarding approval, termination, and eligibility for parallel track protocols.<sup>181</sup> The regulatory process contemplates that the FDA and the NIAID will process requests for ARAC review of parallel track proposals and furthermore that ARAC recommendations will pass through the Directors of NIAID and the NIH on their way back to the FDA.<sup>182</sup> Presumably, this complicated regulatory scheme obtains the benefits of bringing

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177. *See id.* Note that the balancing test involves either eight or eleven factors, depending on enumeration. *See id.*

178. *See id.* Although the provisions regarding Phase II approval and recruitment are listed as a factor in the balancing test, the language of the policy statement implies that this is a mandatory criterion for parallel track status. *See id.*

179. Expanded Availability, *supra* note 169, at 13,251.

180. *See id.* at 13,257. Note, however, that the policy does allow drug sponsors to request non-review by the ARAC in favor of direct consideration by the FDA. *See id.* It is unclear from the policy guidelines whether ARAC involvement is expected to speed-up the drug review process, or instead to slow it down. *See id.*

181. *See id.* at 13,250 (discussing composition of ARAC).

182. *See id.*

outside experts into the drug review process, as well as of making NIAID and NIH privy to decisions about new AIDS drug development. This policy is important because these other agencies own responsibility for supporting the conduct of new drug research showing high promise.<sup>183</sup>

As with the other expanded access and accelerated approval reforms undertaken by the FDA, the parallel track program is not without its share of criticism. Notably, the program does not address the financial issues surrounding treatment access for patients whose indigence or insurance poses an insuperable barrier to payment for experimental drugs.<sup>184</sup> And, although the program guidelines make it possible for parallel track access to occur very early in the drug development process (after the completion of Phase I), it is unclear whether the ARAC review procedure can effectively fulfill the promise of the guidelines. Even presuming that parallel track works as intended to provide more rapid access than would be available through the treatment IND regulations, the fundamental risk-benefit dilemma remains unaltered: Earlier access to experimental drugs leads to increased risk and raises questions about the meaningfulness of informed consent where information about new drugs may be very limited. To some degree, concerns about the parallel track may have become moot: Only one experimental AIDS drug, stavudine, has been made available on the parallel track since the policy was implemented in 1992, and recent congressional testimony by an FDA official indicates that the parallel track has fallen into semi-obsolescence because of accelerated approval and the availability of experimental drugs through “open label” studies.<sup>185</sup> Meanwhile, the risk management policy dilemma that animates the parallel track policy remains an unresolved focus of controversy to the present day.

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183. See *id.* Federal interagency coordination potentially serves to generate synergy in regulation among the several government bureaucracies that are collectively responsible for AIDS research and AIDS drug development. See also NATIONAL CANCER INSTITUTE, *supra* note 50, at 9.

184. See Expanded Availability, *supra* note 169, at 13,253. The parallel track guidelines do indicate that manufacturers may petition the FDA for authorization to charge patients for access to unapproved, parallel track medications, as authorized under 21 C.F.R. § 312.7. See *id.* at 13,254.

185. See *Clinical Trial Subjects: FDA Protections?: Hearing Before the Comm. on Gov't Reform and Oversight*, 105th Cong. 14 (1988) (statement of Michael A. Friedman, M.D., Lead Deputy Commissioner of the Food and Drug Administration). Note that “open label” refers to a variation of the “compassionate IND” procedure, in which treatment access to experimental drugs may be granted to more than one patient at a time. See Cooper, *supra* note 131, at 334.

## IV

THE POLICY DILEMMAS OF EXPANDED ACCESS AND  
ACCELERATED APPROVAL

The FDA's multiple efforts to expand access and accelerate development of AIDS drugs mirrors a shift in the regulatory perspective regarding new pharmaceutical development in the context of life-threatening illnesses. Whereas the traditional mission of the FDA focused on protecting the public against unsafe or ineffective new drugs, the AIDS epidemic and concomitant political activism compelled a grudging administrative recognition that the traditional mission neglected the interests of people whose lives were primarily threatened by the absence of treatment, rather than by unidentified harmful side effects of treatment. By corollary, to the extent that FDA policies delayed and limited experimental treatment access for PWAs, those policies may, inadvertently, have served to impose risk, rather than to protect against it. Thus, the FDA initiatives described in the preceding section of this paper reflect a concrete effort to mitigate the negative effects of new drug regulation and to address the needs of PWAs who faced the prospect of imminent death from untreatable medical conditions. Results from recent empirical studies of the new drug approval process suggest that the FDA's initiatives have genuinely expedited access to new drugs for PWAs.<sup>186</sup>

Regulatory reform, however, is an ongoing process and efforts to modify the new drug approval system have met with continued criticism from a variety of quarters. On the one hand, for people confronting sickness and death from AIDS-related illnesses that remain refractory to treatment with current medications, the pace of new drug development is still too slow, even given FDA efforts to cut years from the development time in the new drug pipeline.<sup>187</sup> On the other hand, even some AIDS activists have questioned whether the FDA has gone too far in abbreviating the new drug development process, and whether the FDA has compromised traditional safety and efficacy standards in the effort to make experimental drugs more widely and more rapidly available.<sup>188</sup> These continuing disputes over FDA policy

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186. See generally Shulman & Brown, *supra* note 149.

187. See generally Maxine Wolfe, *After Ten Years: The Realities of the Crisis, Direct Action, and Setting the Agenda*, Address Before the Conference on AIDS Activism (Mar. 22, 1997), available in <<http://actupny.org/%2010thanniversary/wolfespeech.html>>.

188. See Mathew C. Lovell, *Second Thoughts: Do the FDA's Responses to a Fatal Drug Trial and the AIDS Activist Community's Doubts about Early Access to Drugs Hint at a Shift in Basic FDA Policy?* 51 FOOD AND DRUG L.J. 273, 273-75 (1996).

point to a more fundamental question regarding new drug regulation: whether reform efforts signal a basic change in the way that the FDA does its business, or instead suggest a simple shift in the FDA's tolerance for certain kinds of risks in the face of concerted political pressure. Policy arguments for and against administrative paternalism, personal autonomy, scientific testing, and free market commerce all beg the question whether any approach to regulating new drug development can reasonably achieve an optimal balance among competing social interests.

The above notwithstanding, the regulation of new drugs is ultimately a function of scientific procedures and risk management techniques, as well as of policy decisions concerning the limits of personal autonomy and free market commercialism in a world characterized by imperfect information, iatrogenic medication effects, and externalities in experimental treatment decision making. This section of the paper will explore three aspects of the FDA new drug approval regime in an effort to illuminate the policy implications of reform. First, the paper will examine the clinical trial process as a device for information gathering and the sometimes contradictory demands of pharmaceutical research and medical treatment. Second, it will address the dialectic tension between regulation and personal choice in the free market and the premise that some degree of the former may be a necessary prerequisite to the latter. Finally, the paper will discuss the risk-benefit calculus involved in the regulatory process and the implications of shifting drug-related risks from one group of people to another. In the end, any system for regulating new drug development has to serve some assessment of aggregate social welfare based on implicit assumptions about science, economics, and personal choice. The thesis of this paper is that the FDA needs to maintain rigorous clinical trial standards as a predicate to any meaningful evaluation of risks and benefits in connection with new drugs and that information costs, although valued in the coin of human lives, may nevertheless be a necessary price to pay.

#### A. *Regulatory Reform and the Science of Clinical Trials*

In many respects, the development of new pharmaceuticals is an intensely scientific enterprise. The identification and synthesis of new molecular entities with potentially medicinal characteristics draws heavily on experimental biochemistry and physiology; the initial stages of testing in animals are also empirical in nature.<sup>189</sup> But, the

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189. See *From Test Tube to Patient*, *supra* note 3, at 6-9.

key information in regard to effects in human beings, pharmacodynamics, pharmacokinetics, dose response, and toxicity, can only be fully developed through empirical testing in humans.<sup>190</sup> Such testing raises profound ethical questions in regard to exposing research subjects to possible ill effects that, *ex ante*, cannot be probabilistically evaluated.<sup>191</sup> As formalized under FDA guidelines, human research proceeds through a series of phases aimed at minimizing human exposure to risk at each phase and gradually collecting the safety and efficacy information needed to justify broader exposure in subsequent research. The process is complicated by the elaborate methodologies involved in evaluating drug efficacy in humans. Both research scientists and research subjects are prone to bias and psychologically induced demand characteristics<sup>192</sup> (such as placebo effects) in the context of clinical trials, particularly when scientists or subjects have an investment in the outcome.<sup>193</sup> In consequence, formal trials are almost always controlled and are usually structured “blind”—a methodological device by which subjects are randomly assigned to experimental and control (placebo) conditions, and in which subjects, and usually doctors, do not know which subjects receive the drug and which the placebo. At least in theory, such empirical designs allow for quantification of an experimental drug effect, controlling for any psychological or placebo influences.<sup>194</sup>

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190. *See id.* at 11-12, 15.

191. The Nuremberg Code, a response to the criminal human experimentation of the Nazis during World War II, established the voluntary, informed consent of medical research subjects as the fundamental predicate to the ethical conduct of such research. *See* George J. Annas & Michael A. Grodin, *Medical Ethics and Human Rights: Legacies of Nuremberg*, 3 HOFSTRA L. & POL'Y SYMP. 111, 114 (1999). Note that the clinical trial process always involves some degree of exposure to unknown risks and thereby raises the problem of informed consent. Conservative research methods limit that exposure and thus preserve the meaningfulness of consent.

192. Demand characteristics “refer to features introduced into a research setting by virtue of the facts [sic] that it *is* a research study and that the subjects know that they are part of it . . . . [This is] likely to make subjects highly responsive to any cues . . . .” Elliot Aronson et al., *Experimentation in Social Psychology*, in HANDBOOK OF SOCIAL PSYCHOLOGY: THEORY AND METHOD, 441, 454 (Gardner Lindzey & Elliot Aronson eds., 1985).

193. *See generally* Alan H. Roberts et al., *The Power of Non-Specific Effects in Healing: Implications for Psychosocial and Biological Treatments*, 13 CLINICAL PSYCHOL. REV. 375, 375-91 (1993).

194. Even controlled and double-blind research may not be fully effective in eliminating placebo influences, which are ubiquitous. *See* Fisher & Greenberg, *supra* note 72, at 23; *see also* Seymour Fisher & Roger P. Greenberg, *How Sound is the Double-Blind Design for Evaluating Psychotropic Drugs?* 181 J. NERVOUS & MENTAL DISEASE 345, 345-50 (1993) [hereinafter Fisher & Greenberg, *Double-Blind Design*].

The clinical trial process is an elaborate and very expensive mechanism for gathering information. A priori, it is generally impossible to know whether a potential new drug with promising effects in the test tube will prove equally efficacious *in vivo*, and anecdotal evidence of efficacy outside of controlled trials is notoriously vulnerable to error and bias.<sup>195</sup> Thus, the foundational value of the clinical trial process has been that, however expensive it may be, it nevertheless provides exactly the kind of information that makes more conventional medical decision making possible. Selection of appropriate medical treatment has to be based on some knowledge of the comparative efficacies and toxicities of alternative modes of intervention. Once given such information, it then becomes possible to undertake a rational calculus to identify an “optimal” course of treatment, by employing some pseudo-quantitative, implicitly probabilistic apprehension of how the empirically established properties of different drugs would apply to a specific presentation of illness in a given individual.<sup>196</sup> To the extent that empirically derived information is unavailable, treatment decisions become less “optimal,” and in effect more random. This is a classic variation on the “needle in the haystack” problem—even granted that “effective” treatments exist, the benefits can only be fully realized when information is developed to distinguish them from the universe of ineffective, inert, or toxic alternatives.

The early years of the AIDS epidemic witnessed a collision between the information gathering function of clinical trial research and the medical needs of people struggling against life-threatening illness. From a pragmatic perspective, a person without conventional treatment options is compelled to turn to unconventional ones, even where the likelihood of therapeutic response cannot be estimated. And, when experimental treatment can be obtained only through pharmaceutical research, the unfortunate result is a direct conflict between medical treatment and the clinical trial process: the former aimed at the unqualified preservation of an individual life and the latter focused on information gathering, even when the procedures of experimenta-

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195. See, e.g., Roberts et al., *supra* note 193, at 376-77; Fisher & Greenberg, *supra* note 72, at 7-9; Fisher & Greenberg, *Double-Blind Design*, *supra* note 194, at 345. The first decade of the AIDS epidemic provided numerous examples of anecdotally promising new drugs, which later research demonstrated to be without therapeutic value. See ARNO & FEIDEN, *supra* note 7, at 18-19, 81-82.

196. Of course, there is an important sense in which medical treatment is often non-quantitative, as when multiple drugs are employed in therapeutic combinations for which no formal empirical data exists to demonstrate efficacy. Again, this merely serves to highlight the distinction between medicine and scientific research—the demands of medical treatment are very different from those of knowledge seeking in the first instance. The former practice depends on the latter, but they are not the same.

tion may not serve the best interests of individual research subjects. Consider that for any individual AIDS patient enrolled in a clinical trial, it is always better to receive the “real” drug rather than a placebo, because the “real” drug presumably offers some incremental benefit.<sup>197</sup> In the context of a life-threatening illness such as AIDS, people’s motivation to become research subjects is presumably driven largely by treatment self-interest, rather by any altruistic motive to make a contribution to science. On a related note, some activists have challenged the ethics of a research methodology that gives placebos to desperately ill persons, when a potentially efficacious treatment is readily available.<sup>198</sup>

Clinical trial researchers, on the other hand, often proceed from a very different initial assumption: Experimental drugs typically do not work and procedures like placebo-control and randomization are necessary antecedents for any determination to the contrary.<sup>199</sup> The ethics of clinical trial research have generally been focused on patients’ informed consent to exposure to less than fully quantified risks and have neglected to address patients’ claims of deprivation regarding experimental treatments with unknown therapeutic potential.<sup>200</sup> From a research perspective, the utility of new drugs can only be determined by rigorous empirical methods, absent which there is no basis for believing in the superiority of drug over placebo. Moreover, to the extent that demonstrably effective new drugs are vital to the welfare of PWAs, an argument may be made that the clinical trial process is integral, rather than detrimental, to that interest. This seeming contradiction can be reformulated in game theory terms. Although immediate

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197. It should come as little surprise that some participants in controlled trials for new AIDS drugs actually had their “medications” analyzed, and if necessary supplemented, in order to insure that they were not on placebo. See Nancy K. Plant, *Adequate Well-Controlled Clinical Trials: Reopening the Black Box*, 1 WIDENER L. SYMP. J. 267, 285-91 (1996). Even when the “real” drug does not work, an individual patient may still benefit from taking it. The “real” drug is effectively a lottery ticket, with positive value to the patient even when the likelihood of return on the ticket is small or unknown.

198. See ARNO & FEIDEN, *supra* note 7, at 50-52.

199. One estimate suggested that only five percent of compounds submitted for clinical trial prove to be sufficiently safe and effective to merit FDA approval. See *From Test Tube to Patient*, *supra* note 3, at 11-12, 15. The experimental method generally starts from the presumption of a “null hypothesis” (that the experimental drug does not work), and then proceeds to subject that hypothesis to the possibility for empirical disproof. See SCOTT E. MAXWELL & HAROLD D. DELANEY, *DESIGNING EXPERIMENTS AND ANALYZING DATA* 14-19 (1990) (discussing Popperian deductive framework for experimental research designs).

200. The Nuremberg Code does not directly address the latter issue. See generally Annas & Grodin, *supra* note 191.

access to an experimental drug might always be superior from the standpoint of any individual with AIDS, a world in which all such people make that choice may lead to an equilibrium in which everyone is worse-off. If formal clinical trials genuinely do develop information that is otherwise impossible to obtain, then efforts to improve individual welfare by degrading the research process may ultimately prove to be self-defeating gestures.<sup>201</sup>

Initiatives to reform the new drug approval process have modified the way that clinical trials work, in part by making experimental drugs available outside the trials, and in part by abbreviating the trial process and postponing or eliminating some of the research that would otherwise have been required under law.<sup>202</sup> Two possible effects may result from such reform. One effect is to expand access to new drugs, thereby trading the risks of ineffective or dangerous treatment for the risks of no treatment at all. This sort of risk-trading, by itself, may be desirable on a policy basis, because the possibility for positive outcome may be worth the deliberately accepted risks associated with negative outcome.<sup>203</sup> Another effect of reform, however, might be to sabotage the information-gathering process itself by making controlled trials more difficult to conduct or by degrading the quality of information collected thereby. This latter effect is highly undesirable because it threatens to undermine the systematic reduction of risk through scientific advances in treatment, as well as the rational basis for individual choice among treatment alternatives. Any criticism of controlled trials as an arbitrarily formalistic procedure needs to examine closely the connection between research methodology and the empirical data that research ultimately generates.<sup>204</sup> Continuing efforts at regulatory

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201. See *Prisoners' Dilemma*, CONST. SOC'Y (visited Mar. 29, 1999) <[www.constitution.org/prisdilm.htm](http://www.constitution.org/prisdilm.htm)> (“[The Prisoners’ Dilemma game theory problem] addresses that class of situations in which there is a fundamental conflict between what is a rational choice for an individual member of a group and for the group as a whole.”).

202. See *supra* notes 149-68 and accompanying text discussing expedited access and accelerated approval. The FDA definition of “adequate and well-controlled studies” includes several alternatives to placebo-control empirical designs, including active treatment controls, dose-comparison controls, and historical controls. See 21 C.F.R. § 314.126 (1999). Although the regulation stresses the importance of controlled experimentation as a means for demonstrating drug effectiveness, the regulation clearly does not mandate that research subjects receive inert placebos where there exists an alternative treatment known to be effective.

203. See *infra* notes 219-31 and accompanying text for a discussion of risk regulation in new drug development.

204. Despite liberalization in the clinical trial process, there is continued pressure to make clinical research more responsive to the individual medical needs of research subjects. See Plant, *supra* note 197, at 292-95. Clearly, whenever placebo-control designs can be modified to facilitate medical treatment needs without sacrificing the

reform need to weigh carefully the possible ill effects on research information gathering concomitant to new initiatives to expand access and accelerate approvals.

### B. *Regulatory Reform and Personal Autonomy*

Efforts to reform the FDA's new drug approval regime have focused on making experimental drugs available more rapidly, both on a pre-approval and a post-approval basis.<sup>205</sup> One of the major effects of reform is to place increased decision-making power in the hands of PWAs. Where traditional FDA procedures reserved unto itself exclusive authority to weigh the risks and benefits of experimental drugs, reform has transferred some of that authority to the people who actually bear the risks of and reap the benefits from those drugs. Given that PWAs and people facing other life-threatening conditions already confront grave risks in the form of unavailable medical treatment, an important rationale for reform suggests that those people are better equipped than the FDA to calculate their own risks and benefits from experimental treatment and furthermore that the risks of that treatment depart radically from those that would apply to the wider population.<sup>206</sup> Increasing the autonomy of PWAs is thus desirable both for the instrumental value that accrues to more efficient risk-benefit determinations, as well as for the intrinsic value that derives from the right to make independent decisions.<sup>207</sup> The challenge in reforming FDA regulations to increase patients' autonomy is to avoid what Justice Breyer termed "inconsistency"—the effect of inadvertently increasing risk by neglecting to consider the broader effects of a regulatory initiative.<sup>208</sup> Efforts to serve autonomy interests by short-cutting the FDA drug review process pose several avenues for paradoxical increases in risk that, in the extreme, might undermine the instrumental and intrinsic ends that autonomy serves.

Once again, a major concern in any regulatory effort to increase the autonomy of people seeking experimental treatments for AIDS is

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integrity of data collection, there is an ethical obligation to do so. The proposition, however, that modification does not sacrifice data collection is *itself* an empirical question with no clear answer at present. In consequence, it is not so surprising that some AIDS activist groups have recently pushed for restored methodological rigor in clinical trials, rather than the opposite. *See id.* at 293-95.

205. *See supra* notes 131-83 and accompanying text.

206. That is to say, the general population has less to gain, and more to lose, from wagering on experimental drugs that have not been subjected to the full force of FDA review.

207. *See Salbu, supra* note 10, at 423-28.

208. *See BREYER, supra* note 18, at 21-23.

the potential for negative feedback effects on information.<sup>209</sup> Autonomy, or the right to make one's own decisions, is desirable ultimately because it endows the individual with control over his or her own choices and the ability to make those choices consistent with self-interest.<sup>210</sup> As applied to the domain of medical decision making, the autonomy interest corresponds to an individual's control over bodily integrity, based on personal values and beliefs. Fulfillment of the autonomy interest with regard to experimental drugs therefore requires access to the drugs and information about the consequences of taking the drugs. All other factors held equal, the autonomy interest is at its height when information is perfect, because that is the condition under which an individual can exert greatest control over bodily integrity based on personal values. Conversely, the autonomy interest is weakest, presumably, in the complete absence of information, when an individual has no control over treatment outcome because of ignorance regarding any relationship between personal choice and consequences.<sup>211</sup> The difficulty in promoting autonomy interests through new drug regulation is the possibility that autonomy expanding reform can itself exert a negative impact on information, and thereby sabotage the very interests that it was designed to promote. To the extent that efforts to increase autonomy impede the collection of safety and efficacy data on new drugs or promote experimental treatment decisions in the absence of good information to support them, it becomes unclear whether the autonomy interest has truly been advanced at all.

A related aspect of the same problem involves the externalities that result from patients' autonomy-maximizing choices. Consider the example of the participants in a clinical trial who, uncertain of receiving an experimental drug versus a placebo, break the research protocol by analyzing the composition of their pills, and (if need be) supplementing a placebo with an experimental drug from some other source.<sup>212</sup> As stated earlier, it is always in the individual interest of

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209. See *supra* notes 189-204 and accompanying text discussing science and clinical trial methods.

210. See Salbu, *supra* note 10, at 423-28.

211. One can readily envision an "autonomous" patient in an unregulated market facing a choice among dozens of treatment alternatives, with no clear informational standards, no reliable information, and no basis for making rational choices. This is a very different picture from that which is sometimes asserted in support of maximizing patient autonomy by abolition of the controlled clinical trial process, particularly where uniform access to good information is a priori assumed, and the relevance of clinical trial methods to information gathering is dismissed out of hand. See generally Salbu, *supra* note 10.

212. Again, this is a historical practice for which there is significant anecdotal evidence. See Plant, *supra* note 197, at 285-91.

any particular person to receive the experimental drug, but large-scale defections from the control (placebo) condition may sabotage the results of the clinical trial, perhaps delaying FDA approval by distorting the information that the trial was designed to develop.<sup>213</sup> The externality here is the negative effect on other persons' choices that rounds to the exercise of individual autonomy interests. Of course, the loss of information regarding the new drug may prove deleterious in a number of ways, as by hampering research, limiting access, or making therapeutic effects less clear. But, the key aspect of the externality lies in an exercise of individual autonomy interests that has the effect of making others worse off, and possibly injuring everyone's autonomy interests in the long run. It is precisely this kind of situation in which the government interest in protecting the public welfare may support interventionist regulation, even at some burden to individual autonomy interests.<sup>214</sup> The key is to adopt regulation that protects a maximum level of personal autonomy consistent with aggregate welfare, while ensuring that the regulation itself is not so burdensome as to promote the kind of individual defection described above. This is clearly a very difficult regulatory balance to strike.

Information is not the only aspect of the new drug approval process that is potentially affected by the balance between government regulation and patients' autonomy interests. Manufacturer behavior and commercial development may also be affected, and again in sometimes paradoxical ways. Thus, the traditional NDA process, by erring on the side of conservatism in rigorous research, almost certainly hurts PWAs by creating economic disincentives to development for new drugs, particularly given an immature commercial market in which demand for those drugs is unclear.<sup>215</sup> Expedited development procedures enhance patients' autonomy interests by allowing them to take on greater risks than might otherwise have been allowed. But, there is also a secondary beneficial effect here: expedited development presumably creates an incentive to drug manufacturers by reducing development time and in consequence, development costs.<sup>216</sup> To the extent that autonomy-enhancing measures also serve to encourage commercial investment in new drug research, PWAs receive a double benefit from the FDA reform. On the other hand, the hypothetical

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213. See *supra* notes 197-201.

214. See Salbu, *supra* note 10, at 423-24.

215. See, e.g., ARNO & FEIDEN, *supra* note 7, at 39 (describing initial reluctance of Burroughs Wellcome to undertake development of AZT, in face of uncertainty regarding potential for future profit).

216. See Shulman & Brown, *supra* note 149, at 512-17.

extreme of a completely unregulated market has potentially negative consequences for commercial development, despite the prospect of superficial autonomy enhancement in a world free from FDA interference. Exactly how manufacturers would respond to an unregulated marketplace is unclear; but, given the costs of advertising compared to clinical trial research, it seems plausible that competition might favor reduced research and increased directed marketing, especially in the absence of any government imposed standards for proof of new drug safety and efficacy.

Although government regulation and patient autonomy may appear, at times, to be mutually irreconcilable, each is in some measure dependent upon the other for its fulfillment. The extreme of draconian safety and efficacy regulation is self-defeating not only because such a scheme ignores the costs associated with delayed drug development, but also because such regulation alienates the interests of PWAs, who in the absence of any other treatment options, may defect to black market alternatives uncontrolled by regulation.<sup>217</sup> The opposite extreme of complete patient autonomy in an unregulated market is similarly self-defeating because complete autonomy subordinates the research process to the needs of individual medical treatment, despite the absence of research information required to make medical treatment decisions on a rational basis.<sup>218</sup> As important an interest as patient autonomy is, that interest nevertheless depends on regulatory controls to prevent fraud, promote research, and insure that public goods (such as information) do not fall prey to the externalities of individual decision making. Continuing efforts to reform new drug regulation must guard against superficial autonomy-enhancing provisions with ultimately invidious effects on patient welfare.

### C. Risk Regulation and New Drug Development

FDA regulation of new drug development is at its heart an exercise in risk management. Untested new drugs pose risks to the population in the form of unknown side effects and unwanted toxicities. Regulation serves to protect against those risks by limiting human exposure until the properties of a new drug can be determined. At the same time, people with serious diseases, such as AIDS, face their own set of risks from the progression of their illnesses. For these people, who eagerly await the approval of new medications, risk may attach

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217. Cf. ARNO & FEIDEN, *supra* note 7, at 60-70 (discussing unregulated sources for compounds thought to treat AIDS).

218. Cf. Plant, *supra* note 197, at 285-91 (discussing clinical trials for AZT and attempts by patients to circumvent protocol to maximize individual interests).

more strongly to regulatory delays in approval than to unidentified drug side effects or toxicity. Thus, it is clear from the outset that FDA regulation is not purely risk reducing, but instead involves the shifting of risk as between different possibilities for injury or among different groups of people.<sup>219</sup> The challenge of risk regulation lies in apprehension of the effects of different government interventions on the full spectrum of risks: both those targeted by regulation, and those that might inadvertently be affected by it.<sup>220</sup> Efforts to reform the new drug approval process raise a number of concerns relating to risk, including the breadth of legislative and regulatory vision in considering the possibilities for risk shifting through reform, as well as more fundamental ethical questions regarding government initiatives that transfer risks from one group of people to another. To the extent that FDA reforms have worked, they have arguably done so by recognizing and balancing a more complete set of risks than was acknowledged under the traditional review process.<sup>221</sup>

Consider that the process for new drug approval is perhaps best characterized in terms of a hierarchical series of risk-benefit determinations. Each approval of a new drug, and each phase of each approval, involves an examination of risks based on empirical results from clinical research. But, the regulatory framework within which these decisions are made is also a function of risk-benefit analysis such that procedures for clinical investigation and review serve, ideally, to minimize aggregate risks and to maximize benefits across repeated review proceedings. The obvious question, of course, is risks and benefits to whom and denominated how?<sup>222</sup> The argument of AIDS activists in the 1980s was that the FDA's appraisal of risks and benefits was clearly at odds with that of PWAs themselves and moreover that the procedures for drug approval imposed greater risks than those they protected against.<sup>223</sup> For patients facing the prospect of imminent deterioration and death secondary to untreatable illness, the unavailability of treatment is the foremost risk factor with safety and efficacy risks in connection with experimental drugs comprising a rel-

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219. See Graham & Wiener, *supra* note 12, at 22-25 (discussing analysis of risk-transfer effects).

220. See BREYER, *supra* note 18, at 21-28.

221. See 21 C.F.R. § 312.84 (1999) (addressing FDA risk-benefit analysis in new drug approvals). See also Graham & Wiener, *supra* note 12, at 226, 228-42 (discussing holistic assessment of competing risks).

222. The question of "whom" relates to the politics of risk-shifting between groups of people. The question of denomination relates to inconsistencies in the quantification of risk by different actors or methodologies. See BREYER, *supra* note 18, at 21-22.

223. See generally Lansdale, *supra* note 10, at 427-32.

atively minor concern. Setting aside the question of whether the government has a fundamental inability to approximate the risk valuations of PWAs, there is a clear risk substitution as between potential injury associated with unsafe new drugs, and injury associated with untreated disease. It was this tradeoff that the traditional drug review process proved unable to navigate successfully.

By making experimental drugs more available earlier in the clinical trial process, reforms have endeavored to address the risks associated with non-treatment that result from regulatory delays in drug approvals. Presumably, reforms involved some degree of substitution in favor of the risks associated with unsafe or ineffective drugs—the FDA’s traditional area of regulatory concern. To the extent that, on balance, the risks of harm associated with lack of treatment exceed the risks of harm in connection with minimally tested experimental drugs, the net effect of reform will be positive.<sup>224</sup> How this balance actually works in the real world is far more complicated. Secondary effects of regulation on information gathering have already been discussed, as has the possibility for loss of patient autonomy through measures that superficially appear to enhance it. These effects illustrate some of the difficulties inherent in measuring, even in rough terms, the risk tradeoffs that are involved in regulatory reform. A more profound difficulty presented by risk management involves the transfer of risk between different parties. When the group of people who stand to gain from regulation is different from the group of people who stand to lose, government is forced to confront an ethical dilemma, even assuming that risk in the aggregate will be reduced.<sup>225</sup>

This was the situation that the FDA faced prior to the expanded access and expedited approval reforms of the late 1980s and early 1990s. The traditional FDA drug approval system moved very slowly, protecting the interests of the broader public at the expense of PWAs who were desperate for new treatments.<sup>226</sup> The status quo ante in-

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224. The net risk reduction represents a “technological” shift in the risk frontier that defines the tradeoff between one form of risk and another. See Graham & Wiener, *supra* note 12, at 36-41.

225. The paradigmatic example here is a situation in which the government must choose between destruction (and loss of life) at a dam, or the destruction and loss of life at village that will otherwise be flooded. As between killing one group of people and killing another, the government faces a “Sophie’s Choice” type dilemma. See generally WILLIAM STYRON, *SOPHIE’S CHOICE* (1979).

226. Some have suggested that the traditional FDA system did not even protect the interest of the broader public because delayed approval was ultimately harmful even to the population as a whole. See, e.g., 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, 403-04 (1989).

volved a “risk transformation”<sup>227</sup>—the protection of one group of persons from one form of risk by exposure of a second group of persons to a different form of risk.<sup>228</sup> Fortunately, reform demonstrated that modification of the system focusing on new drugs for life-threatening conditions could ameliorate the risks to PWAs while maintaining consumer protection for the larger public. This was an important lesson that regulatory disaggregation can serve as an effective risk management device. Even so, FDA reform also led to some risk transfer as increased drug access for PWAs also brought increased risk in the form of iatrogenic injury secondary to treatment with experimental medications. Presumably, however, the risks of the new drugs were freely undertaken by the same individuals already bearing the risk from lack of conventional treatment. In a sense, this substitution might be conceived of as an exchange of lottery tickets with PWAs trading for tickets with a superior risk profile. Provided that information is sufficient for meaningful comparison between the “side effects” tickets and the “lack of access” tickets, the exchange is both utility maximizing and autonomy enhancing for PWAs.

There is a threshold question that arises in any regulatory initiative: When should risk be allowed to lie where it falls and when and how should government enter the business of risk redistribution? The evolution of FDA drug approval procedures from 1938 to the mid-1980s reflected a recognition that the risk from unregulated commerce in pharmaceuticals was intermittently catastrophic, at least for those individuals who lost their lives to fraudulent or toxic “medications.” Ideally, FDA regulation might have operated to spread the risks—alleviating catastrophic burdens by means of supervised clinical research, the costs of which might have been evenly distributed in small amounts across the entire population.<sup>229</sup> In reality, much of the burden was borne not by the broader public, but by people with life-threatening diseases incapable of treatment—another catastrophic risk-burden that the FDA neglected to address until the height of the AIDS epidemic. Presumably the spreading of catastrophic risks regulation or insurance is usually justified on the grounds that *ex ante*, everyone is made better off thereby. The argument for risk transfer in the absence of spreading is much more difficult, since it necessarily invokes comparisons of interpersonal utility in the preservation of life. Nevertheless, government is often compelled to make exactly that

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227. See Graham & Wiener, *supra* note 12, at 22.

228. See *id.* at 22-25.

229. This premise is analogous to that of commercial insurance.

kind of argument because inaction in the face of existing risks is no less a regulatory choice than is that of government action.

Justice Breyer has suggested that where risks to human life are very low in the general population, efforts to modify or eliminate such risks may be counterproductive because of perverse effects deriving from the regulatory process itself.<sup>230</sup> Other scholars have noted that the best institutional paradigm for responding to risks involves a careful and comprehensive assessment of all of the implications of alternative courses of action in the attempt to choose an optimal path.<sup>231</sup> The story of FDA reform has drawn on both of these visions. Perversity in new drug approval procedures has, in recent years, given way to a more systemic viewpoint that recognizes the intimate connection between the risks of experimental medication and those of untreatable disease. Notwithstanding the difficulties of quantifying risk, FDA regulation has been modified to allow for increased patient autonomy in selecting which risks to face, presumably to everyone's benefit. Ongoing efforts to undertake additional reforms contest against the intractable tradeoff between risks from untested drugs and risks imposed by information gathering through research. The possibility of additional regulatory refinement in the clinical trial process holds out promise for further reductions in risk for PWAs. The danger, however, remains that overenthusiastic abbreviation of FDA standards and oversight may lead to unforeseen risk transfer effects and paradoxical increases in aggregate public risk.

## V

### RECENT DEVELOPMENTS AND FDAMA

Criticisms of the FDA drug review process, and political efforts to modify it, did not cease with the adoption of the reform measures of the late 1980s and early 1990s. In 1990, a presidential commission led by Dr. Louis Lasagna published its report reviewing the approval procedures then in use for new cancer and AIDS drugs.<sup>232</sup> The Lasagna Commission praised many of the reform initiatives that had been undertaken by the FDA and urged further reforms including: the restructuring of FDA advisory committees; increased interagency cooperation between the FDA, the NCI, and the NIAID; increased reliance on the institutional review board (IRB)<sup>233</sup> process as a potential

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230. See BREYER, *supra* note 18, at 12-19.

231. See Graham & Wiener, *supra* note 12, at 228-42.

232. See NATIONAL CANCER INSTITUTE, *supra* note 50, at 9-10.

233. Most research hospitals and universities possess IRBs that serve to review proposals for research on human subjects so as to insure that ethical guidelines are met.

substitute for FDA supervision of early clinical trial research; and establishment of a policy and oversight committee outside of the FDA to monitor the agency's performance of new drug approvals and report results to the Secretary of the Department of Health and Human Services (HHS).<sup>234</sup> The Lasagna Commission report also addressed aspects of the experimental drug availability problem beyond regulatory delays in the approval process; the report called for substantial increases in FDA funding and for the extension of public and private health insurance coverage to include the costs of experimental drugs.<sup>235</sup> Although the Lasagna Commission issued its final report at a time when activists remained in intense conflict with the executive branch over its response to the AIDS epidemic, the report was manifestly pro-reform in its overtones and many of the recommendations therein were incorporated into the FDA's own regulatory initiatives.<sup>236</sup>

A more extreme set of recommendations emerged from Vice President Quayle's Council on Competitiveness, a committee empowered by President Bush to review federal regulation with the aim of removing unnecessary regulatory burdens.<sup>237</sup> A study of the FDA new drug review process was undertaken from 1990 to late 1991 with high-level participation by officials from the FDA and HHS, as well as other members of the executive branch. Findings were announced in November of 1991 in the form of eleven recommendations for improving and streamlining the FDA review process.<sup>238</sup> Many of the Quayle Council recommendations recapped the earlier proposals of the Lasagna Commission, including the recommendations for increased FDA funding and the substitution of IRB review proceedings for FDA oversight at the initial phase of IND trials. The Quayle recommendations, however, went farther in some important respects, most notably in suggesting that surrogate endpoint procedures should be adopted for use in all clinical trials and not solely for experimental treatments for life-threatening illness and that the FDA should implement a plan for outsourcing NDA reviews to private contractors.<sup>239</sup>

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*See id.* at 9-10. *See also* Ronald Podraza, *The FDA's Response to AIDS: Paradigm Shift in New Drug Policy?* 48 FOOD AND DRUG L.J. 351, 359-61 (1993).

234. *See* NATIONAL CANCER INSTITUTE, *supra* note 50, at iii-vi.

235. *See id.* at vii.

236. For example, the proposal for interagency coordination among the FDA, NCI, and NIAID resembles in part the procedures that were subsequently adopted for the "parallel track" program. *See supra* notes 180-83 and accompanying text.

237. *See* H.R. REP. NO. 102-1050, at 2-3 (1992).

238. *See id.*

239. *See id.* at 4. Note that the Lasagna Commission had also proposed the outsourcing of NDA review as a means to improve the efficiency of the process. *See*

The Quayle proposals generated significant controversy along party lines, with congressional Democrats accusing the Council on Competitiveness of pressing for extra-legal reforms against the better judgment of agency experts, and congressional Republicans defending the Council recommendations as a legitimate response to a longstanding crisis over the delays and costs associated with new drug approvals.<sup>240</sup> The debate reflected increased political concern and awareness regarding the economic and human costs of a lengthy FDA review process, as well as the potential costs of abridging or deregulating that process.

Continuing legislative concerns over, and dissatisfaction with, the new drug review process have been manifest in a series of congressional hearings through the 1990s.<sup>241</sup> Despite FDA reforms to expedite development for drugs intended to treat life-threatening diseases, the delays and costs of FDA review remained generally on the rise, to the collective consternation of manufacturers, consumers and legislators. By 1993, the average development time to FDA approval was about 12 years, at an estimated average cost of 350 million dollars per new drug.<sup>242</sup> Concerns were repeatedly raised regarding the American “drug lag” in approvals as compared to Europe.<sup>243</sup> More specific criticisms were focused on inadequacies in the coordination between the FDA and drug manufacturers in the design of clinical trial research, and on the costly delays to that research associated with “confusing [FDA] communications” and “inadequate [FDA] guidance.”<sup>244</sup> The criticisms of pharmaceutical manufacturers and some consumer advocates, however, were challenged by top officials at the FDA, led by Commissioner David Kessler. Although acknowledging the importance of ongoing FDA efforts to accelerate drug approvals and to improve coordination with the drug companies, Dr. Kessler challenged the empirical basis of the so-called “drug lag” and asserted that there were fundamental limits to accelerating FDA review without abrogat-

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NATIONAL CANCER INSTITUTE, *supra* note 50, at 12. The Quayle Commission report went farther, however, in proposing reduced FDA review authority and limited FDA access to the actual data associated with NDAs. See H.R. REP. NO. 102-1050, at 4. 240. See H.R. REP. NO. 102-1050, at 7-14, 21-24.

241. See, e.g., Statement of Senator Judd Gregg, *supra* note 5, at 14-17; Statement of Congressman Joe Barton, *supra* note 24, at 1-2.

242. See *Drug Efficacy*, *supra* note 23, at 192-95.

243. See, e.g., *Drugs and Biologics: Hearings Before the Subcomm. on Oversight and Investigations of the House Comm. on Commerce*, 104th Cong. 130-35 (1995) (Statement of Kenneth I. Kaitin, Ph.D.); Statement of Fred W. Lyons, Jr., *supra* note 6, at 223-24.

244. *Drugs and Biologics: Hearings Before the Subcomm. on Oversight and Investigations of the House Comm. on Commerce*, 104th Cong. 13-15 (1995) (Statement of Christian W. Nolet, National Director, Life Sciences Industry Group).

ing the agency's commitment to consumer protection and thereby endangering the public welfare.<sup>245</sup> At about the same time, concerns had begun to emerge in some segments of the AIDS community that the FDA had gone too far in its retreat away from traditionally rigorous clinical trial procedures, with the consequence of increasing treatment related risks to PWAs.<sup>246</sup> Pressure and controversy regarding reform at the FDA ultimately sparked legislative action.

A major congressional initiative to overhaul the FDA's statutory mandate culminated in the Food and Drug Administration Modernization Act (FDAMA), which was signed into law by President Clinton in November of 1997.<sup>247</sup> At the broadest level, the FDAMA was designed to "streamline FDA's procedures and strengthen the agency's ability to accomplish its mandate in an era of limited Federal resources," as well as to increase FDA accountability.<sup>248</sup> The FDAMA was a sweeping piece of legislation that amended many aspects of the FDA's enabling statute, the FFDCA.<sup>249</sup>

Several elements of the FDAMA bear directly on the approval process for new drugs. First, Congress adopted into law a set of expanded access provisions, designed to supplement the FDA's regulatory reforms and to emphasize the availability of investigational drugs to patients with serious and life-threatening diseases. The new provisions allow any person, acting through a licensed physician, to request an investigational drug from a manufacturer for personal use, provided that necessary conditions are met.<sup>250</sup> Second, Congress also amended the FFDCA to formalize the "fast track" status for expedited approval of new drugs, authorizing corresponding FDA review procedures based on surrogate endpoint data, and allowing the FDA to commence

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245. See *Revitalizing New Product Development From Clinical Trials Through FDA Review: Hearing on S. 1477 Before the Senate Comm. on Labor and Human Resources*, 104th Cong. 97-127 (1996) (Statement of David A. Kessler, M.D., Commissioner, FDA).

246. See Lovell, *supra* note 188, at 273-74, 279-80.

247. Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (codified as amended in scattered sections of 21 U.S.C.).

248. S. REP. NO. 105-43, at 2 (1997). The FDAMA also served a third major purpose: to renew the Prescription Drug User Fee Act of 1992, an earlier piece of legislation that permitted the FDA to subsidize the costs of drug review by fees levied against applicant pharmaceutical companies. See *id.*

249. See *id.* for an overview of FDAMA's substantive amendments to the earlier FFDCA. A full examination of the terms of the Act is beyond the scope of the current paper.

250. See Pub. L. No. 105-115 § 561, 111 Stat. 2296 (1997). See also S. REP. NO. 105-43, at 76 (describing preconditions to expanded access under statute).

its review prior to the completion of an NDA.<sup>251</sup> Third, Congress framed an explicit mission statement for the FDA, charging the agency both with the protection of public health by product regulation, as well as with prompt and efficient review of clinical research in a manner designed not to impede innovation or product availability.<sup>252</sup> Beyond the foregoing, a number of other provisions in the FDAMA may also influence the new drug approval process, including provisions bearing on increased FDA accountability, interagency coordination, and outside contracting for expert review.<sup>253</sup>

In mid-1999, eighteen months following the passage of the FDAMA, the legislation appears primarily to have impacted the new drug approval process by enacting into statute many of the reforms that the FDA had already undertaken on an administrative basis. The statute, however, also has the aim of improving the efficiency of FDA procedures more generally, and of bringing the agency into compliance with statutory time limits for new product review. The FDA's initial plan for compliance with the FDAMA statute was published as a guidance document in November of 1998.<sup>254</sup> According to the FDA compliance plan, the agency intends to pursue a multi-prong strategy in fulfilling the objectives of the statute, including the establishment of risk based priorities and a systems approach to regulation, as well as strengthening the science base for FDA decision making and improving collaboration with interest groups that have a stake in the agency's decisions.<sup>255</sup> The FDA noted, however, that it faces a number of exogenous challenges, ranging from budget constraints and technology issues to unpredictable new health and safety threats, that will continue to create obstacles to the consummation of legislative expectations for the agency's performance.<sup>256</sup> By and large, the FDA compliance plan is fairly general in its discussion of administrative efforts to reform the agency, and the ultimate effect of the plan on the new drug approval process is unclear, apart from broad initiatives to make FDA regulatory proceedings more transparent, to solicit more collaboration with public stakeholders, to provide regular FDA feedback on

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251. See Pub. L. No. 105-115 § 112, 111 Stat. 2296. See also S. REP. NO. 105-43, at 88.

252. See Pub. L. No. 105-115 § 406, 111 Stat. 2296. See also S. REP. NO. 105-43, at 2.

253. See S. REP. NO. 105-43, at 4-5.

254. See U.S. FOOD AND DRUG ADMIN., FOOD AND DRUG ADMINISTRATION MODERNIZATION ACT OF 1997: FDA PLAN FOR STATUTORY COMPLIANCE (1998), available in <<http://www.fda.gov/oc/fdama/fdamapln.pdf>>.

255. See *id.* at 13-16.

256. See *id.* at 5-9.

its progress in meeting its statutory duties, et cetera.<sup>257</sup> At a minimum, then, the FDAMA has formalized previous FDA measures to improve the new drug approval process, and FDA administrative guidance suggests that the agency will continue to pursue reforms under the statute into the future.

Despite the momentum for liberalization in FDA new drug approval procedures, the prospects for future substantive reform are unclear. On the one hand, the FDAMA reflects the argument of many activists, pharmaceutical manufacturers, and political conservatives that the FDA has long overstepped its bounds through a regulatory regime that was unreasonably oriented toward consumer protection, to the exclusion of legitimate concerns about possible ill effects on desperate patients or on manufacturer innovation. On the other hand, reform has sparked concern both within and outside the AIDS activist community about injuries and deaths associated with inadequately tested new drugs, and concomitant arguments that the FDA should retain its commitment to rigorous clinical trial standards in the face of political pressure to deregulate.<sup>258</sup> At the heart of the debate lies the fundamental risk tradeoff between iatrogenic injury and injury secondary to untreatable disease, between the costs of information gathering and those of ignorance. Past reforms have succeeded by modifying FDA policies to account more fully for the various risks and benefits associated with new drug testing. The best hope for continued progress lies in the FDA's efforts to approach risk management in a systemic way, and to further refine its procedures so as to maintain the integrity of research information-gathering while securing additional reductions in associated costs and risks.

#### CONCLUSION

Over the past twenty years, the story of FDA reform in the new drug approval process is in large measure the story of a consumer protection agency responding to allegations that its own conduct inflicted injuries on consumers. The AIDS epidemic created a situation in which the risks of a conservative drug approval procedure were focused onto an identifiable and politically organized minority group. The protests of AIDS activists served dramatically to make manifest the costs associated with prolonged FDA review of new drugs: costs no less denominated in the coin of human lives than those associated

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257. See *id.* at 3.

258. See, e.g., Lovell, *supra* note 188, at 278-85; see also Paul D. Rheingold, *Fen-Phen and Redux: A Tale of Three Drugs*, TRIAL, Jan. 1998, at 78, 78-83.

with unsafe or ineffective drugs. The FDA reform initiatives discussed in this paper—expedited access, treatment IND, parallel tracking—all operate to make experimental drugs more available to PWAs, while in theory maintaining the information-gathering function of clinical trial research that serves to protect against iatrogenic harms. To the extent that FDA reforms achieve their purposes, they do so by acknowledging and balancing a broader set of risks than was previously contemplated by the agency. Reform also “works” by recognizing that for people with serious or life-threatening disease, decisions about the risks of experimental treatment may best be made by those whose lives depend on it. By corollary, the limits of successful reform are defined by the fundamental ambiguities in “balancing” risks not fully quantifiable, and in the externalities to individual autonomy that may undermine the rational basis for utilitarian decision making.

In this regard, it is noteworthy that one of the primary functions of the FDA review process is the acquisition of information, in the absence of which medical treatment decisions become little better than gambling in a casino. A related focus for criticism of FDA regulation has been that controlled clinical trial methodology imposes an unacceptable and unethical burden to individual patients with life-threatening illnesses.<sup>259</sup> This proposition may be valid where less structured methods can obtain similar information, or where the drug under investigation is known, a priori, to constitute an effective treatment. The proposition, however, is not valid where information is otherwise unobtainable, and where efficacy of the experimental compound is not known in advance.<sup>260</sup> The rationale for controlled human experimentation has always been grounded on the lack of alternatives for collecting requisite information on treatment effects, and on the premise that the conduct of human research is justified when efficacious medical treatment is otherwise nonexistent. Reforms of the clinical trial process that increase experimental drug availability without degrading the collection of information are clearly desirable. But just as regulators must acknowledge the risk of harm to patients associated with lack of treatment, so too must patients acknowledge the harm to medical treatment that derives from the loss of information secondary to the abrogation of the research process. To eliminate clinical trial procedures is to eliminate the scientific basis for medical decision making. History suggests that, far from serving the interest of patient autonomy, the

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259. See, e.g., Lovell, *supra* note 188, at 278-81.

260. Controlled clinical trial research on new drugs is generally conducted precisely because effectiveness is not known in advance.

absence of scientific information creates an environment in which ineffective, fraudulent, or dangerous medications can proliferate.

For this reason, proposals for radical FDA reform by means of stripping the agency of its authority to regulate new drugs are almost certainly counterproductive.<sup>261</sup> The premise that an unregulated free market will produce optimally safe and effective products rests on a series of economic assumptions (such as perfect information and perfect competition), none of which apply to the real world pharmaceutical industry.<sup>262</sup> Even the notion of “risk contracting”<sup>263</sup> between patients and drug manufacturers presumes that both parties to the contract can estimate the product liability risks involved—a problematic assumption, unless the free market recapitulates exactly the kind of empirical information gathering that is currently required by the FDA.<sup>264</sup> Similarly, the suggestion of replacing the mandatory FDA pre-market approval scheme with an elective FDA certification scheme also raises more questions than it answers.<sup>265</sup> Presumably, FDA certification would create a two-tiered market in which the upper tier would correspond to rigorously tested drugs similar to those that pass through FDA review today, while the lower tier would represent everything else.<sup>266</sup> In principle, consumers might benefit from increased access and reduced costs for uncertified new drugs. But in practice, it is far from obvious how the market would respond to a certification system. One could imagine a world in which competition between the tiers would place increasing pressure on manufacturers to do less clinical trial research and to gather less scientific information—a Pyrrhic victory for market forces, at best. Any systemic effort to manage drug-related risks needs to account for the economic disincentives of regulation in regard to the behavior of manufacturers. But, here again, information is a critical precursor to policy concerns about market efficiency. In the absence of scientific information generated

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261. See generally Salbu, *supra* note 10; Gieringer, *supra* note 10. But see Elizabeth M. Rutherford, *The FDA and “Privatization”—The Drug Approval Process*, 50 FOOD AND DRUG L.J. 203 (1995) (discussing ways to modify FDA drug approval regime in order to reap benefits of “privatization” while maintaining consumer protection).

262. See Griffin, *supra* note 27, at 369-78.

263. See Salbu, *supra* note 10, at 422-23.

264. See *id.* at 435-39. Criticisms of the ethics of controlled clinical trial methodology are well-taken, but the premise that statistical meta-analysis or uncontrolled community trials can provide an equivalent information substitute is dubious at best.

265. See Gieringer, *supra* note 10, at 208-53.

266. Drugs in this lower tier would range from new drugs with somewhat less rigorous clinical trial data to support them to quack remedies with no formal testing data whatsoever.

by regulatory standard-setting and review, efficiency in the market for pharmaceuticals becomes an objective impossible of fulfillment.

The FDA new drug review process, as applied to PWAs and to the broader American population, involves the regulation of risks to consumers. In general, the premise of regulation is to minimize (wherever possible) the level of risk exposure, and ultimately to transfer or transform risks in a manner that is both utility maximizing and socially equitable. Unfortunately, government efforts to accomplish these ends are sometimes self-defeating. This is so in part because the regulation of small, low-probability risks can impose very high costs at the margin, often with the effect of creating new risks that exceed the ones originally targeted.<sup>267</sup> A classic manifestation of this kind of effect was the impact of traditional FDA drug review on PWAs. The combination of the regulatory process and an untreatable, epidemic disease led to the imposition of catastrophic risks onto an *ex ante* identifiable group of people—exactly what the regulation was intended to prevent. In contrast to successful, risk spreading devices, which alleviate disastrous risks by imposing costs evenly across the population, the new drug review process served to take one set of disastrous risks and exchange it for another set, undiluted and perhaps even more devastating. Recent FDA reforms have helped to minimize this highly undesirable risk transformation, but the original lesson should not be lost on proponents of future reform, because efforts to control risks by deregulation can also result in paradoxical transformation effects. History bears ample witness to the costs associated with inadequate consumer protection against unsafe and ineffective drugs in the marketplace.

In sum, the current FDA regime for new drug approvals has shifted in order to account better for the interests of those at risk from lack of treatment, as well as those at risk from unsafe or ineffective treatment. This balancing is far from perfect, as evidenced by the criticisms of activists who would expand reforms to apply to drug development more broadly, and by others who would reverse reforms in order to protect people with life-threatening diseases from the potential for iatrogenic harm. Exactly where the lines should be drawn in pre-market requirements for rigorous clinical trial research is unclear. Nevertheless, such research is the informational bedrock that makes risk-benefit determinations possible, whether on an individual or a public policy basis. In speaking of democracy, Winston Churchill

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267. In this regard, Justice Breyer offers an anecdote about how the removal of asbestos fibers likely creates greater health risks than does simply leaving asbestos insulation in place. See BREYER, *supra* note 18, at 12-13.

once described it as “the worst form of government except all those other forms that have been tried from time to time.”<sup>268</sup> The sentiment also applies to FDA regulation of new drug approvals: a costly and evolving process that is nevertheless demonstrably superior to the historical alternatives. It remains to be seen whether continuing efforts to reform the agency will ultimately serve to yield unprecedented new benefits by reductions in aggregate risks, or instead to recapitulate the fundamental dilemma that has so frequently accompanied regulatory initiatives in the past—the paradoxical imposition of risk in consequence of efforts to achieve the opposite.

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268. THE PENGUIN DICTIONARY OF MODERN QUOTATIONS: TWENTIETH-CENTURY QUOTATIONS 80 (J.M. Cohen & M.J. Cohen eds., 1980).