

# Getting New Drugs to People with AIDS: A Public Policy Response to Lansdale

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## Introduction

In an essay published recently in this journal,<sup>1</sup> Bret Lansdale<sup>2</sup> argued that the new drug approval system administered by the Federal Food and Drug Administration (FDA) deprives people with AIDS (PWA) of due process of law. Mr. Lansdale also proposed modifications in that system to speed the delivery of drugs to patients who need them. Although I fully endorse the concept underlying Lansdale's proposals—namely, that patient need for therapy should be considered in the design of drug approval mechanisms generally and in the design of individual drug study protocols—I agree on the basis of sound public policy, rather than on constitutional grounds.

AIDS has already taken a tragic number of lives,<sup>3</sup> and many more are fated to be lost absent a dramatic therapeutic breakthrough. In order for the Fifth Amendment's guarantee of due process to apply to a deprivation of life, liberty, or property, however, there must be a demonstration that the government is responsible for the loss, not just that the loss will occur. Lansdale argues that the government deprives PWA of their interests in life and liberty through its drug approval requirements, which frequently necessitate the use of double-blind placebo-controlled studies<sup>4</sup> to demonstrate the efficacy of the proposed new therapy. In this

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1. Essay, *A Procedural Due Process Attack on FDA Regulations: Getting New Drugs to People with AIDS*, 18 HASTINGS CONST. L.Q. 417 (1991).

2. The essay was written by Bret L. Lansdale, a member of the Hastings College of the Law, Class of 1991, who succumbed to AIDS on October 21, 1990. A memorial to Mr. Lansdale was published with his essay at 18 HASTINGS CONST. L.Q. 257 (1991).

3. As of December 31, 1990, 100,813 Americans had died of AIDS. Essay, *supra* note 1, at 440 n.175.

4. In a double-blind placebo-controlled study, experimental subjects are randomly divided into groups to receive either the drug being tested or a placebo, with neither subject nor investigator aware of who is in which group. It is well accepted that a certain percentage of people will appear to respond favorably to any treatment regimen that they (or their physician) feel will be helpful, whether it is effective or not; this is the so-called "placebo effect." Janssen,

way, "the FDA delays dissemination of helpful drugs and therapies to sick people."<sup>5</sup>

### I. The "Helpful" Drug Fallacy

The deprivation of life and liberty of PWA is predicated on the assumption that the therapies delayed by the FDA are in fact "helpful." The drug development process is complicated and time-consuming; until significant testing has been completed, it cannot be assumed that even the most promising of drug therapies will ultimately be found sufficiently safe and effective to release for marketing.<sup>6</sup>

Drug testing proceeds in a well-established pattern. After a drug sponsor, generally a pharmaceutical manufacturer, has completed laboratory development and animal testing, it seeks FDA approval for human testing by filing a "Notice of Claimed Investigational Exemption

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*The Courts, Terminal Patients, and Unapproved Drugs*, FDA CONSUMER, Nov. 1979, at 5-6. The double-blind design, with a placebo control, enables researchers to distinguish the actual effects of a drug being tested from any placebo effects. See Flieger, *Testing in 'Real People'*, in FROM TEST TUBE TO PATIENT: NEW DRUG DEVELOPMENT IN THE UNITED STATES (An FDA CONSUMER Special Report), Jan. 1988, at 14.

5. Essay, *supra* note 1, at 425. The Federal Food, Drug and Cosmetic Act requires that every new drug introduced into interstate commerce first be proven both safe and effective. 21 U.S.C.A. § 355(d) (West Supp. 1991). The new drug application, or NDA, must include substantial evidence that the drug "will have the effect it purports or is represented to have . . . ." *Id.* "Substantial evidence" is defined by statute to mean

evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have . . . .

*Id.* Neither the statute nor the implementing regulations, 21 C.F.R. §§ 310-314 (1990), requires double-blind placebo-controlled studies. Such studies are, however, the method frequently chosen by investigators of new drug efficacy because they are most likely to provide a clear and convincing demonstration of the test drug's efficacy, and to do so efficiently. FDA personnel state:

It is generally agreed, for example, that the clinical trials of the anti-AIDS drug zidovudine (formerly known as azidothymidine, or AZT) were actually shortened by testing it against a placebo. The studies showed dramatically better results for zidovudine, compared to a placebo, and FDA was able to approve the drug for marketing in March 1987, only four months after receiving an application from the drug's manufacturer . . . .

Flieger, *supra* note 4, at 14.

6. One pharmaceutical company, Upjohn, estimates that only 20 of every 2,000 chemicals studied will ever be tested in humans, and that only one of that 20 will prove safe and effective enough for marketing. The Pharmaceutical Manufacturers of America (PMA), a trade association of research pharmaceutical firms, uses an estimate of one marketed product for every 10,000 chemicals studied. Cohn, *The Beginnings: Laboratory and Animal Studies*, in FROM TEST TUBE TO PATIENT: NEW DRUG DEVELOPMENT IN THE UNITED STATES (An FDA CONSUMER Special Report), Jan. 1988, at 11.

for a New Drug" (IND).<sup>7</sup> After FDA approval, the first human testing, referred to as phase I, begins. Phase I testing, most often done on healthy volunteers, rather than patients, is designed to test a drug's basic safety, to determine its side effects, and, if patient volunteers are used, to gain very early evidence of effectiveness. Phase I studies usually include only 20 to 100 people and take from six months to more than a year to complete.

The limited scope of phase I testing allows only the most tentative conclusions about a drug's safety. A serious adverse event caused by the test drug (such as major organ failure or death) might occur only at a low frequency and thus may not be evident when only a small number of people have taken the drug.<sup>8</sup>

Phase II, which follows successful completion of phase I, involves several hundred patient subjects in studies to determine whether the drug is effective. Although double-blind placebo-controlled studies are not demanded by statute or regulation,<sup>9</sup> they are commonly utilized in phase II and phase III testing to produce data which can support conclusions concerning drug efficacy. Because of the "placebo effect,"<sup>10</sup> phase II efficacy studies must be carefully designed to distinguish the impact of the drug from any improvements in a patient due to non-drug causes. Confounding conditions and events (such as patient ailments other than the drug's target and simultaneous therapy for other health problems) must be kept to a minimum so that researchers can determine whether any improvement seen in test subjects is attributable to the drug itself.<sup>11</sup> Although additional safety evidence is obtained at this stage, a lack of serious adverse effects during phase II still cannot assure safety in wide-

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7. The basic description of drug testing and review which follows may be found in Flieger, *supra* note 4, at 13-17.

8. See Ackerman, *Watching for Problems That Testing May Have Missed*, in FROM TEST TUBE TO PATIENT: NEW DRUG DEVELOPMENT IN THE UNITED STATES (An FDA CONSUMER Special Report), Jan. 1988, at 51.

9. *Supra* note 5.

10. See *supra* note 4.

11. The need to enroll patient volunteers who fit particular demographic and health status criteria has been a subject of considerable irritation in studies of AIDS drugs, see Essay, *supra* note 1, at 425, because drug tests have been perceived by PWA as one hope for survival. Because of the nature of AIDS—an immune deficiency which itself does not kill, but allows other infections the opportunity to thrive and thus to kill—the potential volunteer population is subject to a variety of ailments, some of which may be considered disqualifying for participation by drug researchers. In addition, drug research has tended to use fairly narrow demographic parameters (e.g., white males). To the extent that narrow definitions make it difficult to recruit patient volunteers, studies are delayed; common sense suggests that when this happens the parameters should be broadened. In recognition of the need to test drugs on volunteers representative of the potential patient user population, FDA has issued clinical pharmacology guidelines which require studies in "pertinent populations." Interview with Dr. Roger Williams, Director of the Office of Generic Drugs, Federal Food and Drug Administration (Mar. 17, 1991).

spread distribution.<sup>12</sup>

If phase II is successfully concluded<sup>13</sup>—a process which takes from several months to two years—phase III begins. Phase III consists of expanded trials, both controlled and uncontrolled, to gather additional safety and efficacy information, as well as to collect data about such matters as optimum dosage amounts and schedules, from several hundred to several thousand patients. This phase generally takes from one to three years. Even phase III may not uncover adverse affects that occur at very low frequency. Approval of the sponsor's New Drug Application (NDA) after this level of testing, however, presents a level of risk that scientists and policymakers feel is appropriate if a drug's efficacy has been demonstrated. Naturally, more risk is tolerated in approving a drug marketed for a serious or deadly condition than one marketed either for an annoying but not life-threatening symptom or one which substitutes for safer available therapy.<sup>14</sup>

Thus, a drug that has completed only phase I testing, or even phases I and II, or that has completed phase III testing but has not yet been subject to independent scrutiny,<sup>15</sup> may well not be "helpful." Although it is tragically true that people with AIDS may be dead "long before the FDA allows a new drug to be dispensed at all,"<sup>16</sup> drugs that are not efficacious will not have saved anyone. As therapies such as AZT<sup>17</sup> become available to slow the progress of AIDS,<sup>18</sup> at least in some patients,

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12. Flieger, *supra* note 4, at 14.

13. Approximately 70% of experimental drugs tested in humans proceed from phase I to phase II; about 33% reach phase III. Approximately 25 to 30% of drugs tested in humans will successfully conclude phase III, and about 20% will receive approval to be marketed. Flieger, *supra* note 4, at 14.

14. Lowry, *A Scientist's Viewpoint*, in *HOW SAFE IS SAFE? THE DESIGN OF POLICY ON DRUGS AND FOOD ADDITIVES* 110-11 (1974). Lowry relates that some observers felt that the Salk polio vaccine had been prematurely introduced; if there had been further testing an incident involving 260 injuries from improperly manufactured vaccine might have been avoided. But the two or three year delay "would have resulted in 100,000 cases, or more, of paralytic poliomyelitis. It was known ahead of time that this was true, and the risk was taken deliberately." The ratio of polio cases prevented to polio cases attributable to early release of the vaccine was 400 to 1. "The benefit was rightly judged to far exceed the risk." *Id.* See also *United States v. Rutherford*, 442 U.S. 544, 556 (1979).

15. Drug testing is organized and carried out by the drug sponsor, which is most often the pharmaceutical company that intends to market the drug, and which thus has a major financial interest in obtaining marketing approval. The FDA's scrutiny is the only independent review of the study data. Flieger, *supra* note 4, at 13.

16. Essay, *supra* note 1, at 428.

17. AZT is an inaccurate acronym for the anti-AIDS drug zidovudine, which was formerly known as azidothymidine. See *supra* note 5. As it is the name by which the drug is popularly known, it will be used throughout this article.

18. Longevity for persons diagnosed with AIDS today has clearly increased over the longevity experienced in the early 1980s. The increase in longevity, however, reflects not just the availability of AZT and other anti-viral drug treatments. Because there are better diagnostic tools, PWA are obtaining the AIDS diagnosis earlier in the course of their illness. It is difficult

and with AIDS research producing large numbers of potential drug therapies,<sup>19</sup> most of which will prove to be ineffective,<sup>20</sup> the protection of consumers from ineffective drugs becomes ever more critical.<sup>21</sup> Patients subjected to ineffective drugs may suffer side effects or adverse reactions that hasten their physical deterioration (perhaps even killing them), or make them poor candidates for later effective therapy.<sup>22</sup>

## II. The Inapplicability of Due Process

Even if we accept the premise that the FDA is preventing helpful therapies from reaching sick people, existing case law does not support the conclusion that the FDA's failure to approve or to make available particular drugs more quickly is a violation of constitutional due process. The cases of government inaction giving rise to constitutional violation that are cited to support Lansdale's thesis are distinguishable because the persons deprived—a prisoner in *Estelle v. Gamble*,<sup>23</sup> an involuntarily committed mentally retarded person in *Youngberg v. Romeo*<sup>24</sup>—were themselves unable to supply the needs withheld by the government because of their institutionalization by the government. As Professor Tribe notes, "it plainly requires a further step to conclude that governmental indifference"<sup>25</sup> to suffering, in contexts not involving the confinement by the government of the sufferer, violates a constitutional requirement. The Supreme Court has not yet taken that step. Although we believe, as does Tribe, that "government has affirmative duties to its citizens arising out of the basic necessities of bodily survival,"<sup>26</sup> we must recognize, as he

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to separate these two factors in order to make precise comparisons between the life expectancy of a PWA diagnosed in the early 1980s and one diagnosed today. The average life span for a person diagnosed with AIDS today is approximately 14.2 months. Telephone interview with the AIDS Office, San Francisco Department of Public Health (March 15, 1991).

19. As of February 1991 the FDA had received more than 330 INDs for prevention, diagnosis or treatment of AIDS. Pharmaceutical Manufacturers Association Newsletter, Feb. 18, 1991, at 6.

20. If AIDS therapies follow the pattern of other experimental drugs, it is expected that no more than 20% will be marketed. *Supra* note 13. In light of the huge number of submissions for AIDS therapies it seems likely that a considerably smaller percentage will be found to be either effective or drugs of choice.

21. "There are very few conditions, not even AIDS, that can't be made worse. For example, in the clinical trials of the once-promising AIDS drugs HPA-23 and suramin, the chemicals turned out to be so toxic that the studies had to be ended." Young, *Experimental Drugs for the Desperately Ill*, in FROM TEST TUBE TO PATIENT: NEW DRUG DEVELOPMENT IN THE UNITED STATES (An FDA CONSUMER Special Report), Jan. 1988, at 24-25.

22. See Barry, *A Perspective on Compassionate Parallel Category C Treatment Track IND Procedures*, 45 FOOD DRUG COSM. L.J. 347, 351 (1990).

23. 429 U.S. 97 (1976).

24. 457 U.S. 307 (1982).

25. L. TRIBE, AMERICAN CONSTITUTIONAL LAW 1335 (2d ed. 1988).

26. *Id.* at 1337. Professor Tribe would plainly favor the recognition of such a right, in line with "the governing premise of this chapter—that active governmental imposition or con-

does, that such duties are not legally enforceable at the present time.<sup>27</sup>

scious governmental neglect differs qualitatively from the passive coercion that shapes life generally." *Id.* at 1335 n.39. That he would be especially sympathetic to Lansdale's argument is obvious from his further statement that "relief against unjust indifference need not always take the form of active assistance by government; at times such relief may require only that government relax its otherwise reasonable regulations to accommodate acute instances of need." *Id.*

There is no judicial support, however, for Professor Tribe's position. He admits that the government's duty to meet human needs, other than through procedural safeguards, *id.* at 1336, is enforceable "in the streets and at the polling booth," *id.* at 1337, not primarily in the courts.

The absence of judicial support for this position was also noted by Judge Legge of the U.S. District Court for the Northern District of California when, on December 3, 1990, he turned down an AIDS patient's request for an order reversing the FDA's ban of the sale of a new drug which had not received premarket approval. *Woodroof v. Mlecko*, No. C 90 3377 CAL (N.D. Cal.), minute order filed Dec. 19, 1990. *Cf. DeVito v. HEM, Inc.*, 705 F. Supp. 1076 (M.D. Pa. 1988). The plaintiff and others had been purchasing Peptide T, an amino acid compound used to treat AIDS-related dementia, from its manufacturer when the FDA classified it as a "new drug" and required that it be subjected to premarket approval. Judge Legge concluded that "AIDS patients do not have a statutory or constitutional right to take new drugs that are not approved by the FDA." He called the situation "heart-rending," and stated his belief that "once a person is diagnosed as terminally ill . . . he ought to have the right to obtain most any drug he believes would help alleviate the situation." But, he added, "that is not the law." *Doyle, AIDS Patient Loses Challenge to Drug Ban*, *San Francisco Chron.*, Dec. 4, 1990, at A4, col. 1.

The case was later voluntarily dismissed at the request of the plaintiff. The plaintiff expected to obtain continued access to Peptide T under 21 C.F.R. § 312.36 (emergency use of an investigational new drug); according to plaintiff's attorney he was unable to obtain such access until March 1991. Telephone interview with Michael Cascino, Esq. (March 21, 1991). (The probable reason for the delayed access is that the first major clinical study of Peptide T began in March 1991. Hilton, *Surprises in the War Against HIV*, *San Francisco Exam.*, Mar. 31, 1991, at B-4, col. 1.) In *DeVito*, *supra*, defendants, concluding it was not efficacious in treating AIDS, had terminated clinical studies of Ampligen. Plaintiff's suit to continue using the drug was dismissed for lack of subject matter jurisdiction. Citing *United States v. Rutherford*, 442 U.S. 554 (1979), the court found no exemption from drug approval provisions for terminally ill patients. *DeVito*, 705 F. Supp. at 1079-80. *See infra* text accompanying notes 28-31.

27. Lansdale cited, with hope, Justice Brennan's dissenting opinion in *DeShaney v. Winnebago County Dep't of Social Servs.*, 489 U.S. 189, 203 (1989). Even if Justice Brennan had prevailed in *DeShaney*, and even if he were still sitting on the Court, the factual distinctions between the case of Joshua DeShaney and that of people with AIDS seeking access to unreleased experimental drugs would not assure a constitutional decision in favor of the latter. Justice Brennan's analysis of Joshua DeShaney's plight parallels quite closely the common law doctrine that a person under no obligation who voluntarily undertakes to rescue has a duty to continue the rescue when his or her actions or agreement to assist cut the victim off from other sources of aid. *Id.* at 205-07. People with AIDS are not cut off from *other* sources of aid by the FDA, and not left in a *worse* predicament than they otherwise were; admittedly the lack of any hope other than an effective drug therapy makes this legal distinction ring quite hollow. It is, however, relevant that the assistance that could have been provided to Joshua DeShaney—removing him from his father's home where he was being abused—would have prevented the harm that befell him. In stark contrast, quicker access to experimental drugs by PWA could result in more net harm than benefit.

Justice Brennan further complained that the Court failed to "see that inaction can be every bit as abusive of power as action, that oppression can result when a State undertakes a vital duty and then ignores it." *Id.* at 212. In proceeding with the review of drugs that could

Another significant barrier to successful challenge of the FDA's regulatory authority in the area of approval of experimental therapies is *United States v. Rutherford*.<sup>28</sup> That 1979 case challenged the FDA's authority to prevent terminally ill cancer patients from obtaining Laetrile, a drug not approved by the agency but claimed by its supporters to be safe and effective in cancer treatment. In a unanimous decision, the United States Supreme Court held that there is no implicit exemption for the terminally ill from the premarket approval requirements of the Food, Drug and Cosmetic Act.<sup>29</sup> There was no constitutional challenge before the Court. Commenting on the policy rationale for the statute, the Court noted that to deny the relevance of the proof of safety and efficacy criteria for terminal patients "is to deny the Commission's authority over all drugs, however toxic or ineffectual, for such individuals. If history is any guide, this new market would not be long overlooked."<sup>30</sup> As to the terminal patient's need for protection, the Court stated, "For the terminally ill, as for anyone else, a drug is unsafe if its potential for inflicting death or physical injury is not offset by the possibility of therapeutic benefit."<sup>31</sup>

### III. The Need for Change

Although the FDA's drug approval procedures are not subject to successful challenge on constitutional or statutory grounds, this does not diminish the validity and power of the arguments for change raised by Lansdale and widely advocated among the AIDS patient and support community. In order to evaluate fairly the need for change and to determine how it might be accomplished, it is necessary to understand the nature of the FDA, the regulatory agency charged with the critical task

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be used to treat PWA, the FDA is engaging in just the type of vital duty which Justice Brennan contemplates. Its failure to act as quickly as we might like—or even its negligent conduct of drug review—does not, as Justice Brennan himself recognizes in *DeShaney*, rise to the level of a due process violation. *Id.* at 211.

28. 442 U.S. 544 (1979); see also Janssen, *supra* note 4.

29. *Rutherford*, 442 U.S. at 551.

30. *Id.* at 557.

31. *Id.* at 555-56. The Court added, "it is often impossible to identify a patient as terminally ill except in retrospect." *Id.* at 556. Although the *Rutherford* Court expressed the concern that cancer patients would be harmed by relying on Laetrile, an unproven remedy, in lieu of conventional treatments, which would be efficacious to some, if not all, cancer sufferers, *id.* at 556, that concern was only a minor factor in the Court's determination that drug approval laws are applicable to drugs for the terminally ill. The Court's holding was based instead on statutory interpretation. See *id.* at 551. Thus the precedential value of the *Rutherford* holding cannot be ignored because there are conventional treatments that may cure cancer, whereas there are no curative treatments for AIDS. Further, it is likely that a significant percentage of cancer patients who sought to use Laetrile had already exhausted available conventional therapies without arresting the progress of their cancer. In that respect a significant number of cancer patients are in the same predicament as PWA: without any remedy except hope for the as-yet-unproven.

of overseeing the nation's drug supply.<sup>32</sup>

The first statute regulating pharmaceutical drugs was the Food and Drug Act of 1906, passed at the behest of Dr. Harvey Wiley, Chief Chemist of the Department of Agriculture, who was concerned about the risks of untested chemicals in food and drugs. He dramatized this risk by assembling a "poison squad" of department volunteers to test chemicals on themselves. The statute did not, however, provide for premarket approval of drugs.<sup>33</sup> Premarket proof of safety was first required by the Food, Drug and Cosmetic Act of 1938, which is still in force today. Congress passed that law in response to the deaths of more than 100 people from the drug Elixir Sulfanilamide, which had been created by adding the solvent diethylene glycol (a deadly poison used as antifreeze) to the miracle drug sulfa to make it available in liquid form. Apparently no one bothered to test the solvent's safety.<sup>34</sup>

The Drug Amendments of 1962 added the requirement that drugs also be proven efficacious before marketing. These amendments were passed in the emotional aftermath of another drug tragedy, the thalidomide disaster.<sup>35</sup> Thalidomide, a mild sedative, caused phocomelia, the foreshortening of the limbs, in thousands of babies exposed to it *in utero* in European countries where it had been approved for sale.<sup>36</sup> Americans were spared this disaster as a result of the premarketing proof of safety requirement.

Approval of Thalidomide's NDA had been prevented here by Dr. Frances O. Kelsey, an FDA medical officer.<sup>37</sup> The episode is important in understanding the nature of the FDA and its response to AIDS. Dr. Kelsey was hailed for saving Americans from the harm caused by

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32. Particularly in the earlier years of the AIDS epidemic there was a tendency by people and institutions affected by AIDS to portray those with a different perspective on the problem as villains. The FDA has been subject to such portrayal and to protest on the grounds of a laggardly pace of regulatory response to the crisis. *See, e.g., Police Arrest AIDS Protesters Blocking Access to FDA Offices*, L.A. Times, Oct. 11, 1988, at 2, col. 3. A critical look at the response of various individuals and institutions to AIDS demonstrates that many could have done much better. Some were ignorant, some frightened, some disbelieving. And some were villains. For a general view of the early years of AIDS, which provides a more than adequate supply of villains, see R. SHILTS, *AND THE BAND PLAYED ON: POLITICS, PEOPLE, AND THE AIDS EPIDEMIC* (1987).

33. Janssen, *Outline of the History of U.S. Drug Regulation and Labeling*, 36 FOOD DRUG COSM. L.J. 420, 426-27 (1981).

34. Letter from Frank E. Young, Commissioner of Food and Drugs, and John A. Norris, Deputy Commissioner of Food and Drugs (Jan. 1988), *reprinted in FROM TEST TUBE TO PATIENT: NEW DRUG DEVELOPMENT IN THE UNITED STATES* (An FDA Consumer Special Report), Jan. 1988, at 2.

35. *Id.*

36. Janssen, *supra* note 33, at 437.

37. Thompson, *Protecting 'Human Guinea Pigs'*, in *FROM TEST TUBE TO PATIENT: NEW DRUG DEVELOPMENT IN THE UNITED STATES* (An FDA Consumer Special Report), Jan. 1988, at 20 (not citing Dr. Kelsey by name).



thalidomide.<sup>38</sup> To those who work<sup>39</sup> with her as decisionmakers about new drug approval at the FDA, she is a powerful reminder that the FDA drug review staff is a critical barrier between American consumers and drug-related disasters. The staff member who prevents a disaster will be remembered. In contrast, to approve use of a drug courts disaster, and there seems to be no mechanism to laud those who shepherd a drug to early approval.<sup>40</sup> It may well be that the FDA employees' self-perception—whether conscious or not—as a barrier against drug-related disasters is an important factor in the FDA's overall conservative nature.

To a large extent it is appropriate for the FDA to be conservative or even to be "obsessed with risk,"<sup>41</sup> as was recently claimed. Only the FDA's review of data generated by manufacturers protects consumers from inappropriate approval of drugs. The approval of a drug has vast economic consequences,<sup>42</sup> and although improprieties have been remarkably few they have not been absent.<sup>43</sup> In addition, over time FDA drug

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38. Dr. Kelsey received the Distinguished Federal Civilian Service Award from President John F. Kennedy on August 7, 1962. Telephone interview with Wallace Janssen, FDA Historian (March 13, 1991).

39. Dr. Kelsey continues to work at the FDA as Director of Scientific Investigations, Office of Compliance, Center for Drug Evaluation and Research.

40. The FDA now institutionally encourages expedition in drug review, and the role of scientist reviewers in the approval process is recognized as crucial. Norris, *Fulfilling FDA's Vision of Faster Drug Review*, in FROM TEST TUBE TO PATIENT: NEW DRUG DEVELOPMENT IN THE UNITED STATES (An FDA CONSUMER Special Report), Jan. 1988, at 7. But no reviewer's name is connected with AZT's approval, for example, as Dr. Kelsey's name is linked with keeping Thalidomide off the market. No specific action has been taken, if in fact any is possible, to modify reviewers' incentive to be cautious. Telephone interview with Dr. Roger Williams, *supra* note 11.

41. Henninger, *Will the FDA Revert to Type?*, Wall St. J., Dec. 12, 1990, at A16, col. 4. This editorial writer blames the "obsession" on Congress, Ralph Nader, and the media:

over the past 75 years occasional, highly publicized accidents involving drugs have given congressmen a pretext to announce, with the cameras rolling, that the agency is too sloppy with risk. . . . Naderlike groups would identify risks from particular drugs, and supportive newspaper reporters in Washington would vilify the FDA and offending drug companies for "negligence."

42. For example, if the experimental drug tacrine (Cognex) is approved for improvement of memory in Alzheimer's disease patients, annual sales by sponsor Warner-Lambert are estimated to be \$1 billion or more. The firm's current annual prescription drug sales are only about \$1.6 billion. *FDA Panel Rejects Alzheimer's Drug*, San Francisco Chron., Mar. 16, 1991, at A7, col. 3.

43. *Maker of Generic Drugs Accused of Duping FDA; U.S. Says Bolar Swapped Products, Hid Data*, Wash. Post, Oct. 27, 1990, at A13; *Generic Drugs Recalled After Questions on Data*, N.Y. Times, Feb. 1, 1990, at D2, col. 5; *Wall Street Illustrated*, FIN. WORLD, Sept. 16, 1986, at 149 (Richardson-Merrell indicted for supplying falsified data to FDA about MER-29); She-non, *Lilly Pleads Guilty to Oralflex Charges*, N.Y. Times, Aug. 22, 1985, at A16, col. 1; see *Examination of the Pharmaceutical Industry, 1973-74, Joint Hearings before the Subcomm. on Health of the Comm. on Labor and Public Welfare and the Subcomm. on Admin. Practice and Procedure of the Senate Comm. on the Judiciary*, 93rd Cong., 1st and 2d Sess. Part 7, at 2827 (1974) (statement of John Nestor, M.D.).

approval personnel have perceived undue pressure from drug companies (as well as from their own superiors) to approve drugs, even when unresolved concerns remained in their minds.<sup>44</sup>

In the 1970s an influential group of commentators raised a cry about a "drug lag." They argued that Americans were being denied, or allowed only delayed access to, valuable drug therapies that were available overseas.<sup>45</sup> Consumerists did not share this view; they were concerned about drugs being marketed before safety issues were adequately resolved, and found FDA conservatism laudable, if not insufficiently protective.<sup>46</sup> Furthermore, most new drugs (almost two-thirds of those approved by the FDA in 1990, for example)<sup>47</sup> do not represent any significant therapeutic gain. For those drugs, a cautionary "lag" may well be to the great advantage of the American public.<sup>48</sup> Since the 1970s a number of "blue-ribbon commissions" have studied the drug approval process.<sup>49</sup> Typically they have found the new drug approval system "fundamentally sound," but its implementation in need of considerable improvement.<sup>50</sup> In response, FDA commissioners have vowed to take action.<sup>51</sup> In recent years the FDA has decreased its approval time significantly.<sup>52</sup> Nevertheless, drug development and approval remains a time-consuming process; the FDA expects the development time even for a lifesaving drug to be

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44. See *supra* note 43; see also U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, FINAL REPORT OF REVIEW PANEL ON NEW DRUG REGULATION 31-32 (May 1977) [hereinafter FINAL REPORT].

45. Stone, *Staff Paper: Economic Effect of New Drug Regulation in the United States*, U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, INTERIM REPORT OF REVIEW PANEL ON NEW DRUG REGULATION 19-23 (May 31, 1977).

46. "As protectors of the public, . . . [FDA medical officers] have to be extremely cautious . . . ." Testimony of Sidney Wolfe, M.D., and Anita Johnson, Esq., Public Citizen Health Research Group, before the Review Panel on New Drug Regulation, U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, REVIEW PANEL ON NEW DRUG REGULATION 2-3, 2-7 (May 7, 1975).

47. *Faster FDA Action on 23 New Molecular Entities Approved Last Year*, Pharmaceutical Manufacturers Association Newsletter, Jan. 7, 1991, at 1 [hereinafter *Faster FDA Action*].

48. The official FDA position in 1974 was that a drug lag existed in that drugs were marketed overseas that were not available in the United States but, "when reviewed in perspective, the drug lag did not involve any drugs that represented important therapeutic gains and was an expected consequence of the high regulatory standards imposed under United States law." Hutt, *Investigations and reports respecting FDA regulation of new drugs (Part II)*, 33 CLINICAL PHARMACOLOGY AND THERAPEUTICS 674, 675 (1983).

49. *Id.*

50. *Id.* at 677. See, e.g., FINAL REPORT, *supra* note 44.

51. See, e.g., U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, REPORT BY THE COMMISSIONER OF FOOD AND DRUGS ON FINDINGS AND RECOMMENDATIONS OF THE REVIEW PANEL ON NEW DRUG REGULATION (March 1978).

52. In 1990 FDA reviews of NDAs for new molecular entities (the most important class of proposed new drugs) took an average of 28.1 months as compared to 32.5 months for 1989 approvals. *Faster FDA Action*, *supra* note 47.

approximately five to seven years.<sup>53</sup>

The AIDS crisis has appropriately brought a patient-advocate voice into the main regulatory arena for the first time.<sup>54</sup> The earlier outcry by some cancer patients seeking to use Laetrile is distinguishable.<sup>55</sup> Laetrile proponents were seeking access to a product which no reputable pharmaceutical manufacturer was proposing, even as an experimental therapy. Cancer patients in the "mainstream" of the health care system have since 1976 had access to the investigational drugs that the National Cancer Institute considers most promising.<sup>56</sup> Through a mechanism called the "compassionate IND," the FDA has long allowed experimental drugs to be distributed to patients with no available alternative therapies who were otherwise ineligible for the drug studies.<sup>57</sup>

AIDS patient-advocates have severely attacked the methods used to test drugs for approval, the slow pace of the drug approval system, and the unavailability of promising experimental therapies to a broad group of patients.

PWA are, in Lansdale's words, "wager[ing] their lives"<sup>58</sup> by partici-

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53. AZT's development time of two years is considered quite extraordinary, and probably a record. Studies done by the FDA suggest that the average total development time (which includes preclinical research, and laboratory and animal studies done prior to human testing) for drugs worldwide is eight or nine years. In the United States, the comparable figure is considered to be seven or eight years in general, and five or six years for a product of biotechnology. The PMA's general estimate of 12 years is discounted by the FDA because it includes drugs developed by firms overseas, which encounter significant delays in finding American development partners for their products. Telephone interview with Paul Coppinger, Deputy Director, Office for Policy and Evaluation, FDA (Mar. 25, 1991).

54. The drug companies, which stand to profit significantly from faster approvals of their products, have kept a rather low profile during the debates about FDA procedures fueled by AIDS activism. There are undoubtedly multiple reasons for their stance. First, drug companies have liability concerns about premature marketing of products. Second, it would be unseemly for drug companies to urge (profitable) earlier approval, especially since they have been attacked by the AIDS activists for the pricing of AIDS therapies that have been approved. See Chase, *AIDS Activists Press Boycotts of Drug Firms*, Wall St. J., Mar. 8, 1991, at B1, col. 3.

55. See *United States v. Rutherford*, 442 U.S. 544 (1979); see also Gup, *Doctor's Unusual Treatment Supported by Cancer Patients; Patients Support Doctor Barred by Area Hospital*, Wash. Post, Sept. 28, 1979, at B1; Jolna, *Parents Defy Mass. Court Order, Take Child to Mexico for Laetrile*, Wash. Post, Jan 27, 1989, at A3.

56. These are known as "Group C Drugs." See Anticancer Drug Development; Memorandum of Understanding with the National Institutes of Health, 44 Fed. Reg. 25,510 (1979).

57. See 21 C.F.R. § 312.36 (1990).

Some "compassionate INDs" have been granted for patients excluded from protocols for demographic reasons. Children, for example, are generally not included in studies (unless the drug is primarily for pediatric use), in large part because of the ethical complication of children's inability to consent themselves to the experimental risk. The compassionate IND mechanism has also been used to make experimental drugs available to test volunteers (and others) between the end of studies deemed successful and the approval of the drug's NDA. See generally 52 Fed. Reg. 19,476 (1987).

58. Essay, *supra* note 1, at 431.

pating in double-blind placebo-controlled studies because they may be randomly selected to receive not the test drug, but a placebo. Prior to the approval of AZT, the use of placebo-controlled studies was justified because there was no available therapy with any proven effectiveness to treat AIDS; volunteers who received a placebo were not foregoing the opportunity to receive effective treatment. Now that AZT is available, it would be unethical to design a drug study including patients for whom AZT is an appropriate therapy, yet withhold that proven drug and offer only a placebo to one group, thus risking their lives unnecessarily.<sup>59</sup>

Lansdale and others have urged that researchers use methods to test AIDS therapies that do not require an untreated ("placebo") control group. There has been increased flexibility in study design in recent years, presumably because of the requirements of medical ethics as applied to individual test subjects and because the research community realizes the plight of PWA.<sup>60</sup> On the other hand, it is still necessary to design studies that will efficiently yield adequate evidence of effectiveness. Thus, in at least some drug tests, researchers must include appropriate control groups and apply demographic and health-status criteria to the selection of volunteers.<sup>61</sup>

The speed of drug approval has also accelerated, largely in response to the AIDS crisis.<sup>62</sup> Although the FDA has long classified experimental drugs by their potential therapeutic importance<sup>63</sup> and directed its attention disproportionately to the more important applications, it has now adopted specific regulations on the expedited development, evaluation, and approval of drugs intended to treat life threatening and severely debilitating illnesses.<sup>64</sup> One important feature of the regulations, recom-

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59. FDA officials indicate that it would be virtually impossible at this time to design a placebo-controlled AIDS drug study in which the volunteers were not allowed to take AZT. Studies of the drug dideozinosine (ddI) have proceeded without a placebo control group. Alternative methodologies (such as using a "run-in" phase in which one group begins drug use before the others) have been created to substitute for placebo-controlled studies because of the ethical considerations. Interview with Dr. Roger Williams, *supra* note 11. See Essay, *supra* note 1, at 422-35.

If the study drug would be toxic when taken with AZT, the only available alternative treatment, a study design which is both ethical and scientifically appropriate could be elusive. If volunteers are sought who can no longer tolerate AZT, the testing might all be done in a patient group whose disease has progressed too far for a fair evaluation of the investigational drug.

60. Interview with Dr. Roger Williams, *supra* note 11.

61. Flieger, *supra* note 4, at 12.

62. The crisis-response nature of the changes in FDA procedures is not surprising given the past history of drug regulation in this country. See *supra* notes 33-36 and accompanying text.

63. Schwinghammer, *FDA's Rating System for New Drugs*, Pharmacy Update, Jan. 14, 1991, at 8.

64. 21 C.F.R. §§ 312.80-312.88 (1990) (Drugs Intended to Treat Life Threatening and Severely-debilitating Illnesses).

mended by blue-ribbon commissions and previously implemented informally, is early consultation between the drug sponsor and FDA officials concerning study design.<sup>65</sup> Consultative meetings serve to prevent the delays that occur when FDA reviewers discover after the fact that completed studies have not yielded information needed for approval.<sup>66</sup> The most dramatic change under these regulations, though, is that the FDA would approve drugs for marketing after phase II in return for the sponsor's agreement to conduct so-called phase IV studies, postmarketing studies to obtain additional information which could not be discovered during phases I or II.<sup>67</sup> AZT was reviewed under expedited approval procedures, and was available on the market in only two years, after phase II.<sup>68</sup>

In 1987 the FDA adopted regulations regarding treatment use of investigational drugs (the "Treatment IND").<sup>69</sup> These regulations essentially institutionalize and streamline the "compassionate IND" process to meet the needs of PWA as well as others. Drugs with the potential to treat serious or immediately life threatening diseases in patients with no comparable or satisfactory alternative therapy may now be made available for treatment, as contrasted with experimental use during phase III studies and, in appropriate circumstances, during phase II studies. A "Treatment IND" will be approved if there is evidence that the drug may be effective or that it will not expose patients to unreasonable and significant additional risk of illness or injury. Drug companies may charge for, but may not profit from, Treatment IND distribution. This innovation makes drugs available to patients who are not eligible for experimental protocols, which is a significant concern of the AIDS community. From 1987 to 1990, nineteen drugs were made available under the Treatment IND regulations, of which six were for AIDS-related conditions.<sup>70</sup>

While generally applauded, the Treatment IND procedures have been criticized as not allowing early enough distribution of potentially useful drugs for AIDS therapy. In 1990 the FDA responded with a policy statement setting up what it calls "parallel track" procedures for drug

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65. Such consultation can take the form of oral and written communications as well as agency guidelines. FINAL REPORT, *supra* note 44, at 39-44, 66-71.

66. Farley, *Benefit vs. Risk: How FDA Approves New Drugs*, FROM TEST TUBE TO CONSUMER: NEW DRUG DEVELOPMENT IN THE UNITED STATES (An FDA CONSUMER Special Report), Jan. 1988, at 29.

67. 21 C.F.R. § 312.82(b) (1990); Young, *The Reality Behind the Headlines*, in FROM TEST TUBE TO PATIENT: NEW DRUG DEVELOPMENT IN THE UNITED STATES (An FDA CONSUMER Special Report), Jan. 1988, at 5.

68. Young, *supra* note 67, at 5.

69. 21 C.F.R. §§ 312.34-312.38 (1990).

70. Telephone interview with Winnie Piper, FDA AIDS Coordination Staff (March 25, 1991). Controversy has recently erupted over paperwork requirements for receiving access to two experimental drugs, DDC and clarithromycin. Chase, *supra* note 54.

testing.<sup>71</sup> Under this mechanism, created only for AIDS and HIV-related diseases, drugs would be made available for treatment purposes when the evidence for effectiveness is even less than that required for a Treatment IND. The criteria would include promising evidence of efficacy, evidence that the drug is reasonably safe, sufficient data to recommend an appropriate dose, evidence of a lack of alternative therapy, and assurance that the treatment availability would not interfere with the recruitment and retention of patients for controlled clinical trials. By choosing to structure this proposal solely for the AIDS crisis, the FDA is demonstrating its recognition that regulatory mechanisms can and should be flexibly tailored to the public's need.<sup>72</sup>

Although these structural changes in the drug approval system appear responsive to appropriate concerns raised by Lansdale and others, their implementation nevertheless raises significant questions, particularly in regard to informed consent. One major impetus for a patient to enroll in a drug study is the possibility of obtaining helpful therapy before it is otherwise available. If, under parallel track or Treatment IND procedures, one can obtain an investigational drug without having to risk being placed in a non-treatment or alternative drug control group, why enroll in a study? To obtain the informed consent of study volunteers, it seems proper to inform them that they may be able to get the experimental drug without being in the study. This is somewhat of a circle, however, because drugs cannot be made available under the Treatment IND or parallel track rules unless the necessary clinical studies are successfully recruiting study volunteers.<sup>73</sup> Ethicists will need to face the conundrum that adequately informing potential volunteers of alternative distribution possibilities may risk their willingness to be in studies—and simultaneously risk the availability of the alternative distribution.

Researchers have also expressed concerns about these early release programs. They fear that enrollment in studies might be adversely af-

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71. 55 Fed. Reg. 20,856 (1990).

72. Young, *supra* note 67, at 5. Cynics would add that FDA appears to be demonstrating its recognition that street demonstrations, *see supra* note 32, would not end until it took such action. The FDA actions are in line with Professor Tribe's suggestion that "relief against unjust indifference . . . may require only that the government relax its otherwise reasonable regulations to accommodate acute instances of need." Tribe, *supra* note 25, at 1335 n.39. And they demonstrate the accuracy of Tribe's assertion that some governmental duties are enforceable "in the streets." *Id.* at 1337. The success of political action by the AIDS community has spawned attempts to organize similar action among other patient groups. *See Beck, The Politics of Breast Cancer*, NEWSWEEK, Dec. 10, 1990, at 62.

73. 55 Fed. Reg. 20,858 (1990) (assessment criteria for parallel track approval include "the impact that the parallel track study may have on patient enrollment for the controlled clinical trials and a proposed plan for monitoring progress of the controlled trials"); 21 C.F.R. § 312.34(b)(iii) (1990) (one criterion for treatment IND approval is that the "drug is under investigation in a controlled clinical trial under an IND in effect for the trial, or all clinical trials have been completed").

fect, and completion of controlled clinical trials threatened (as by dropout of patients who prefer to obtain the test drug in the parallel track).<sup>74</sup> In addition, some are concerned about the increased risk of harm from drugs released earlier in the development process.<sup>75</sup>

These new mechanisms created by the FDA, especially the parallel track, address Lansdale's compelling argument that government response to a deadly epidemic disease of unprecedented proportions cannot proceed in a vacuum. Generally speaking, the American system of drug approval has protected American consumers very well. For those to whom an experimental drug on the horizon is the only ray of hope in a desperate struggle for life, requirements of science and of bureaucracy, of caution and of regulation, seem at best illogical and at worst cruel. Nevertheless, sound public policy supports both the FDA's initiatives making possible earlier distribution of experimental drugs and the continuation of a scientifically sound, drug approval system that protects the patient.

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74. Cooper, *Changes in Normal Drug Approval Process in Response to the AIDS Crisis*, 45 FOOD DRUG COSM. L.J. 329, 336 (1990).

75. Peskoe, *Application of AIDS-Related Drug Approval Processes to Other Drug Therapies—A Different View*, 45 FOOD DRUG COSM. L.J. 357, 359 (1990).

