

New Rules for New Drugs: The Challenge of AIDS to the Regulatory Process

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THE AIDS EPIDEMIC, SUDDENLY AND SYSTEMATICALLY, is transforming American attitudes and practices about the regulation and use of drugs. In the 1970s, as psychiatrist Gerald Klerman (1974) astutely observed, Americans were pharmacological Calvinists and psychotropic hedonists, that is, ever so cautious and sparing about the drugs they took in the pursuit of health, and ever so open and daring about the drugs they took in the pursuit of pleasure. This orientation had rather odd effects not only on personal behavior (a reluctance to go on an antibiotic, no reluctance to try the newest sensation-expanding compound) but also on the direction of public policy. With a minimum of intellectual discomfort liberals simultaneously advocated that the government keep its regulatory hands off pleasure drugs (for example, legalize marijuana and heroin) and expand the authority of the Food and Drug Administration (FDA) so that, as we shall see, drugs like thalidomide would be kept off the market. Now, in the 1980s and in the tide of the AIDS epidemic, these attitudes are being reversed. In the case of AIDS, the response is pharmacological hedonism—a willingness to try any drug with the whisper of a chance to halt the deadly progress of the infection—and there may be an insurgent psychotropic Calvinism—a mounting insistence on the fact that drugs can kill, indeed that pleasure (including sexual pleasure) is dangerous. And once again, these attitudes are re-

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structuring policy. They encourage, at one and the same time, a war on drugs and a war on the FDA and other regulatory bodies—like the institutional review boards (IRBs)—that stand between the consumer and the drug manufacturer. In the course of this article, we will be focusing on the pharmacological side of this dualism, leaving to others to ponder the changes that AIDS may be bringing to psychotropic (and sexual) hedonism. The transformation in the pharmacological arena is of such critical dimensions as to well warrant full attention.

The Drug Control Model

The regulatory system that underlay the pharmacological Calvinism of the 1960s and 1970s was born of scandal. The enlarged authority of the Food and Drug Administration and the creation of the institutional review boards were both the result of widely perceived abuses on the part of drug manufacturers and biomedical researchers. It appeared as though the greed of the one and the ambition of the other was so unbounded that government had to intervene to protect the consumer/human subject. As against the dangers of a hands-off policy, the exercise of governmental paternalism seemed altogether justified.

The transforming moment in the history of drug regulation was 1962. Senator Estes Kefauver was winding up a long and only modestly successful campaign to regulate drug prices by demonstrating that the companies were reaping unconscionably huge profits. The companies' justifications notwithstanding, including considerable investment in new drug research and development, Kefauver insisted that the consumers were bearing an unfair burden (*Congressional Record* 1962a). But however impressive the testimony that he elicited, no changes in the law seemed likely to emerge from the hearings, at least until the thalidomide story broke. This drug, widely prescribed in Europe, was in the process of being evaluated for safety by the FDA. One official, Frances Kelsey, concerned by reports of peripheral neuropathy, delayed approval, and in the interim the link between thalidomide and birth defects (typically, warped limbs) became apparent. Kelsey later received the highest award for government service from President Kennedy (Lasagna 1989). Although a major catastrophe had been averted, some 20,000 Americans, of whom 3,750 were of child-bearing age and 624

were reported as pregnant, had already taken thalidomide on an "experimental" basis. These experiments were more part of drug company marketing efforts to persuade physicians to use the drug than bona fide efforts to test it. To make matters worse, the precise number of recipients was unknown and their identification incomplete, mostly because the companies and the prescribing physicians who were conducting the trials kept very sloppy records.

Kefauver took full advantage of the incident and the harsh light it shed on drug company practices to clinch the case for greater regulation. In fact, his case now became so compelling that the proposed legislation passed both the House and Senate unanimously (*Congressional Record* 1962a). Yet as often happens, the scope of the response far exceeded the nightmare case that provoked it. The Food, Drug, and Cosmetic Act (FDCA) changed drug-approval procedures from premarket notification to premarket approval. Before 1962 new drugs could be marketed after the pharmaceutical sponsor submitted safety data unless the FDA reviewed the data and said no; after 1962 the FDA had affirmatively to say yes, thus giving FDA staff reviewers and the advisory committees more responsibility for the decisions. Congress also required the FDA to evaluate drugs not only for safety (an authority it held since 1938) but for efficacy as well—even though efficacy was not an issue in the case of thalidomide (Lasagna 1989).¹

The entire episode demonstrates how powerful the symbolic role of a nightmare case can be in the implementation of public policy. Sustaining the drug regulatory enterprise between 1962 and the AIDS crisis was the figure of an heroic Frances Kelsey, single-handedly saving Americans from tragedy by saying no to a drug manufacturer. The message was clear: those who exercise caution reap rewards; there were no prizes for government employees who said yes to a drug, no matter how effective it turned out to be. Moreover, this message was one to which the FDA staff was especially receptive, for those recruited to these positions, at salaries substantially below those in the private sector, were very likely to arrive with a sense of mission about consumer protection. Thus, it is not surprising that the FDA defined its goals after 1962 in terms of minimizing risk. Its purpose was to assure the safety of marketed products, leaving it to others like the National Insti-

¹21 U.S. Code sect. 355(b) as amended by P. L. 87-781, sect. 102(b) (1962).

tutes of Health (NIH), to worry about curing disease. The FDA, in brief, had every incentive to avoid what statisticians call type 1 errors even at the price of type 2 errors of greater magnitude. Better to err on the side of safety, even if it meant keeping an effective drug off the market for a longer period.

Controls on Human Experiments

The development of regulatory authority over human experiments follows a similar and overlapping course. In the hearings and debates on the Kefauver bill, the senators learned, to the amazement of at least some, that patients who received experimental drugs in these preliminary trials did not always know that they were participants in an experiment and that the safety of the drug had not been established. New York's Senator Jacob Javits, profoundly disturbed by this finding, proposed an amendment to the Kefauver bill which would have compelled the Secretary of Health, Education, and Welfare to write regulations that "no such drug may be administered to any human being in any clinical investigation unless that human being has been appropriately advised that such drug has not been determined to be safe in use for human beings." As Javits explained: "I feel deeply that some risks must be assumed. . . . [Nevertheless,] experimentation must not be conducted in a blind way, without people giving their consent. . . . Where is the dignity, the responsibility, and the freedom of the individual?" But Javits's colleagues were unwilling to accept his proposal. In this early moment in the history of public policy and bioethical issues, they conflated experimentation with therapy and the investigator with the physician. They believed, for example, that requiring physicians to inform a patient about an experimental drug would also compel them to inform a patient about a diagnosis that was fatal (in 1962 an unthinkable principle), for it might happen that to get the patient to take the new drug the doctor would have to tell him that he was suffering from a life-threatening illness. With a "strict, mandatory, prenotification requirement," argued Florida's Senator Carroll, "we might prevent the doctor from helping his patients in times of extreme emergency" (*Congressional Record* 1962b). In effect, there seemed little reason to glove the hand of the researcher or deny patients/subjects the miracles of the laboratory.

But soon, once again as the result of scandals and whistle-blowers, this reluctance disappeared and the researcher became the object of widespread suspicion. The transforming moment was Henry Beecher's (1966) article in the *New England Journal of Medicine* on the ethics of human experimentation. At its heart were capsule descriptions of twenty-two examples of investigators who risked "the health or the life of their subjects" without informing them of the dangers or obtaining their permission. Example 2 constituted the purposeful withholding of penicillin from servicemen with streptococcal infections in order to study alternative means for preventing complications. The men were totally unaware of the fact that they were part of an experiment, let alone at risk of contracting rheumatic fever, which twenty-five of them did. Example 16 involved the feeding of live hepatitis viruses to residents of Willowbrook, a state institution for the retarded, in order to study the etiology of the disease and attempt to create a protective vaccine against it. In example 17, physicians injected live cancer cells into twenty-two elderly and senile hospitalized patients without telling them that the cells were cancerous, in order to study the body's immunological responses. Example 19 described how researchers inserted a special needle into the left atrium of the heart of subjects, some with cardiac disease, others normal, in order to study the functioning of the heart (Beecher 1966; Rothman 1987).

Beecher's most significant, and appropriately most controversial, conclusion was that "unethical or questionably ethical procedures are not uncommon" among researchers, that a disregard for the rights of human subjects was widespread. The twenty-two cases, he declared, had been too easy to compile; an earlier and longer draft of the article had a total of 50 which had to be winnowed down for publication (Beecher 1966).

The *New England Journal of Medicine* article captured an extraordinary amount of public attention. Accounts of Beecher's piece appeared in the leading newspapers and weeklies, and dismay was mixed with incredulosity as reporters, readers, and public officials alike wondered what led respectable scientists to commit such acts (Faden and Beauchamp 1986, chaps. 3-4). The impact was even more noticeable at the National Institutes of Health, the major funding agency of biomedical research. Dependent upon congressional funding and good will for its budget, the NIH had scrupulously to consider the implications of the exposés for its own operation. At least one congressman

had written the NIH to inquire how it intended to respond to Beecher's cases, and its associate director hastened to assure him that the findings "as might be expected have aroused considerable interest, alarm, and apprehension," and that "constructive steps have already been taken to prevent such occurrences in research supported by the Public Health Service" (PHS) (Sherman 1966).

The congressman's letter was only the most visible sign of the NIH's vulnerability (or sensitivity) to political and legal pressure. Any Washington official who hoped to survive in office understood the need to react defensively, to have a policy on hand, so that when criticism mounted he would be able to say that, yes, a problem had existed, but procedures were already in place to resolve it. The NIH director, James Shannon, readily conceded that one of his responsibilities, even if only a minor one, was "keeping the government out of trouble." And his advisers concurred: it would be nothing less than suicidal to believe that "what a scientist does within his own institution is of no concern to the PHS" (Frankel 1973, 23). An ad hoc group appointed by Shannon to consider NIH policies reported back that if cases involving researchers' disregard of subjects' welfare came to court, the service "would look pretty bad by not having any system or any procedure whereby we could be even aware of whether there was a problem of this kind being created by the use of our funds" (Frankel 1973, 31).

The result of all of these elements was the creation of a collective mechanism whereby individual researchers had to obtain the approval of their peers—and of at least some representatives of the wider community—before they could conduct experiments that put humans at risk. By the mid-1970s, the NIH (and the Public Health Service) had in place a system whereby every institution that received their research funds had to organize an institutional review board to pass on each protocol. The IRB's principal assignment was to insure that the risks to the research subject did not outweigh the benefits, and that the subject had been informed of all the significant aspects of the research (including the right to withdraw from the experiment at any time), and had voluntarily consented to participate. Along with the IRB regulations came a series of specific rules and proposals that sought to protect the most vulnerable classes of subjects, that is, the once competent and the never competent (the institutionalized mentally ill and retarded, children, and the elderly) and prisoners. These groups had been the subjects in a majority of the protocols in Beecher's roster of dishonor, and

the new regulations made it difficult, at times impossible, to use them in experimentation. Once the NIH-PHS system was developed, the FDA came aboard, requiring that protocols testing drugs on humans also secure approval from the IRBs (*Federal Register* 1971).

Thus, overlapping regulatory systems were established on the dual premises that drug manufacturers were unreliable, motivated more by profits than concern for the consumer, and researchers were untrustworthy, motivated more by ambition than by concern for the patient. Put another way, the definition of the problem that underlay the government response, the cases that came to mind when regulations were written, were of thalidomide and Willowbrook, the former justifying the apparatus of the FDA, the latter, the apparatus of the IRB.

Following this orientation, these two regulatory systems shared a number of special characteristics:

First, the FDA and the IRBs both relied heavily on a standard of "sound science," hopeful that its postulates would rein in the ambitions of pharmaceutical companies and individual investigators. In the ethics of human experimentation, this precept had been announced by judges in rule 5 of the Nuremberg Code: "The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problems under study that the anticipated results will justify the performance of the experiment" (*Trials of War Criminals before the Nuremberg Military Tribunals* 1949, vol. 2, pp. 181-82). The rule's contemporary embodiment became the federal regulation declaring that IRBs must review research to assure that procedures are consistent with "sound research design" and do not unnecessarily expose subjects to risk. The IRBs must also assure that "risks to subjects are reasonable in relation to anticipated benefits."² Thus, bad science is unethical science. Yet, the tension between the norms of pure science—which relies heavily on the individual investigator's skepticism about conventional wisdom—and the authority of regulatory bodies, including nonscientists, to decide what constitutes good science went unnoticed, at least outside the corridors of research institutions.

Similarly, the role of "sound science" became central to the FDA's administration of the drug control model even as it had a paradoxical relation to the real world of medical practice. The law prohibits anyone

²45 *Code of Federal Regulations* sect. 46.111(a)(2) (1988).

from introducing into commerce a "new drug" unless the drug is covered by an approved "new drug application"(NDA).³ The FDA can approve such an NDA only if the drug is safe and if substantial evidence from adequate and well-controlled trials demonstrates that the drug is effective.⁴ Safety and efficacy are measured in relation to the drug's utility in treating the particular diseases delineated in the drug's proposed labeling. The labeling becomes, in effect, an FDA-approved indication for the drug's use. During the 1960s and 1970s, the FDA demanded that drug manufacturers prove drug efficacy by multiple controlled clinical trials. Indeed, insisting on strict "scientific proof" of efficacy proved to be the vehicle by which the FDA accomplished the burdensome task, imposed on it by the 1962 Kefauver amendments, of reviewing the thousands of "new drugs" that had reached the market under NDAs from 1938 and 1962, when safety alone was the test; it revoked permission to market after a group of experts had determined that scientific proof of "efficacy" was lacking. By taking the position that manufacturers were not even entitled to a hearing unless there was evidence of efficacy derived from controlled clinical trials, the FDA avoided the necessity of time-consuming administrative hearings for hundreds of drugs. At such hearings doctors could have been expected to testify about all the patients a drug had helped in the course of their practices, and the pharmaceutical companies could claim this evidence "proved" drug efficacy. Such anecdotes are not evidence, the FDA ruled; data are not the plural of anecdote. The administrative task was accomplished, therefore, by delegitimizing uncontrolled physician experience as a basis for permissive regulatory action. The law required scientific proof, and science required that drug efficacy be established through very exact and well-defined methods.⁵

However, neither science nor law controls what doctors do once the drug is on the market. Physicians can prescribe the drug for whatever purposes and in whatever doses they wish, subject only to whatever constraints are imposed by, for example, fear of malpractice suits or hospital pharmacy controls. The FDCA regulates commerce, not the practice of medicine. It is common, therefore, for drugs to be used for

³21 U.S. Code Annotated sect. 355(a) (West Supp. 1989).

⁴21 U.S. Code Annotated sect. 355(d) (West Supp. 1989).

⁵*Weinberger v. Hynson, Wescott and Dunning, Inc.* 412 U.S. 609, 612 (1973).

a much wider range of indications than "scientific evidence" supports. Physicians do their own "cost-benefit" analysis of new drugs once the compounds reach their hands, exercising the very type of professional discretion which, after 1962, was no longer the standard for gaining FDA drug approval. Thus, the insistence on scientific standards made securing an NDA an even greater economic prize, bringing rewards for successful drug innovation that even Kefauver could not have imagined. Obtaining a NDA gave the pharmaceutical companies a market not only for the listed indications, but, through physician discretion, a market, often much broader, for unlisted indications. More, obtaining an NDA may deter a competitor's entry with a different drug, unless the competitor is willing to incur heavy research and testing costs while facing a smaller market and is ready to run the risk that the FDA may not judge a second drug "safe" unless it has some advantage over the one already marketed.

Second, the new regulatory system assumed that being a research subject was a burden that should be distributed as equitably as possible. The premise was that human subjects were at risk, that taking part in an experiment was a sacrifice, and that sacrifice should be made by all, not just the helpless in society. So consent forms originally composed in English had to be translated into Spanish if the population to be recruited was heavily Hispanic, and if the form was not translated, for whatever reason, these subjects were not to be used.

Third, the system was prepared to make the trade-off of slower medical advances in return for better monitored ones. In the context of human experiments, the price was largely unacknowledged. Not only were the financial costs of the monitoring hidden in overhead and indirect cost allocations afforded to the research institution, but the possible social costs in slowing down or discouraging an individual investigator were very difficult to quantify or aggregate. In the context of drug review, however, the FDA's oversight did come in for withering attacks from both the pharmaceutical industry and a number of academicians. Their central complaint was that it cost too much and took too long to secure approval of a new drug. These critics posited a "drug lag," and argued that the incredible increase in the average length of time and costs in securing marketing approval for a new drug—from a couple of years and a few million dollars in 1960 before the Kefauver amendments to an average of ten years and nearly \$100 million in the 1970s—undercut company incentives. The reduction explained the

sharp drop in introduction of "new chemical entities" for pharmaceutical use. A variant on the drug-lag theme was that useful drugs first reached the market in Europe, because European nations' standards were more realistic, meaning that United States citizens received second-best care while the FDA procrastinated about possible side effects. Perhaps most poignantly, regulatory costs created therapeutic orphans, persons whose diseases or situations were sufficiently rare that it simply did not pay to produce therapies directed to them, even if one had a therapy that probably worked (Schifran and Payan 1977; Wardell 1973).

This is not the place to evaluate the accuracy of the drug-lag claims. Suffice it to say, they are hotly contested (Schmidt 1974). What is most important for our purposes is not the critique's validity but rather its premises and the nature of the FDA and congressional responses. For one, the critique of the FDA came in the name of cost-benefit analysis, not of consumer rights. The distinction is important. Those who objected to a reputed "drug lag" did not want to make drug law akin to securities law, where issuers can sell anything, even "bonds" they themselves claim to be "junk," so long as the prospectus properly discloses the situation. No one was urging that the consumer be left to decide among untested drugs. For another, most critics did not challenge the hierarchical control of decision making about drug therapies; they accepted the role of scientific expertise and the randomized clinical trial to evaluate efficacy. The major objection was to the use of these trials, at great expense, to ascertain the likelihood of remote side effects. Moreover, Congress generally sided with the FDA. Its main legislative response was the creation of the orphan drug program, attempting to ameliorate the problem by providing special incentives to produce drugs for small markets. Congress believed that it was not relaxing the overall standards for drug approval, but, as we shall see, the innovations in orphan drug regulation, particularly FDA participation in protocol design and expanded therapeutic use of nonapproved drugs, served as the model for changes in the AIDS era.⁶

The *fourth* characteristic of the regulatory system in the 1960s and 1970s was the adversarial posture of the regulator toward the regulated. Since the drug company was "suspect," the proper stance for the FDA was to be critical and suspicious, not collaborative. It was not the role

⁶21 U.S. Code Annotated sect. 360bb (West Supp. 1989).

of the FDA, for example, to recommend that particular drugs be tested or to cooperate in the design of the trial. It was to be nondirective, the umpire who rules on the products developed, not a player in the game.

All of these considerations contributed to what may well be the most extraordinary fact about the drug and experimentation regulatory process: in a period when autonomy and rights were the highest values in almost every aspect of medical and health care delivery, this was one particular area in which heavy-handed paternalism flourished. Over the 1960s and 1970s, whether the context was truth-telling or the right to refuse treatment, the emphasis was on the right of the individual to make his or her own decision. Social ideology and, to an unprecedented degree, social policy reduced the discretion of those who, by virtue of their expertise, professional position, or community position, had been accustomed to making decisions on behalf of others; the list of those who suffered this loss includes college presidents and deans, high school principals and teachers, husbands and parents, prison wardens and social workers, psychiatrists, hospital superintendents, and mental hospital superintendents (Rothman 1978). But the strength of this movement notwithstanding, it was still the experts on the FDA and the IRBs, and not the patient or the subject, who decided in the first instance whether the risk/benefit ratio with a new drug or experiment was acceptable. Just when patients were securing the right to know their own diagnoses and to decide whether to accept or reject treatment, the FDA and the IRB secured the right to decide for patients and subjects whether they might try a new drug or might enter a new protocol. In essence, the arena of drugs and experimentation was an island of ideological paternalism in a sea of autonomy, running counter to the trends that swept over American medicine in the 1960s and 1970s.

The Attack on the Drug Control Model

The friction between the paternalism of the drug control model and the post-1960s commitment to individual rights smoldered rather than burned in public policy consciousness. Political life is filled with such instances, where one generation's premises lose their cultural resonance, while the bureaucratic rules and procedures they spawn continue on nonetheless, sustained indefinitely not by the strength of their ratio-

nales but by their familiarity to the affected groups. It requires a crisis of an unprecedented intensity to force the incongruities to a new synthesis.

AIDS provided this very crisis. The HIV epidemic has produced a sustained attack on the premises and structure of drug regulation and human experimentation. Advocates for the gay community and persons with AIDS have reacted with fury to the slow pace at which experimental therapies for the disease were sought out and initiated. As they see it, a few cases of Legionnaires disease and a couple of poisoned Tylenol capsules produced the scientific equivalent of a five-alarm fire. AIDS, by contrast, claimed neither notice nor effort, and the shortfall was bitterly felt. Apparently, gay lives did not matter; worse yet, they might well be intentionally sacrificed to reinforce the new conservatism's call for a return to "traditional values and lifestyles." As a result, a coalition of AIDS advocates put forward positions that were in fundamental opposition with those that had dominated the earlier debate (see Appendix Note). The outcome was a consumerist approach to therapy and a powerful critique of the drug approval process. If the government and the pharmaceutical industry were laggard in researching new therapies, then the affected community was obligated to organize itself to track down every therapeutic possibility no matter where in the world it might appear, and do everything that it could to make that drug available to its members. Moreover, persons with AIDS and their advocates reject the paternalism and risk-averse attitudes of the FDA-IRB establishment (Delaney 1989; Eigo et al. 1988). It is fascinating to recall that a mere eight years ago, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research focused public attention on the ethical dilemmas of trying out new cancer drugs. At congressional hearings, ethicists questioned whether researchers had not gone too far in encouraging patients' participation in "treatment" protocols for advanced cancer where there was no likely prospect that the therapy would long delay death. To be sure, all the patients were volunteers, but was it proper to let people in extremis volunteer for "treatment" protocols when no reasonable prospect of cure existed? (U.S. Congress 1981). One will not see in the current literature on AIDS any comparable concern with whether it is ethically justified to employ experimental treatment protocols to increase, however marginally, the life expectancy of infants with AIDS.

The AIDS activists find it not only appropriate to launch initiatives

to locate new drugs, but also to declare it the right of patients to have unrestricted access to these new experimental therapies (AIDS Coalition To Unleash Power [ACT UP] 1989). The fact that a therapy has not been "proved" through the canons of "good science," they assert, does not mean that access to it must be restricted, or indeed that insurers may reject claims of payment for it. Moreover, persons with AIDS reject the IRB notion that the marginal and easily exploited in our society should be protected from the risks of participation in experiments. Experimental treatment is not a burden but a form of treatment, and persons have a right to treatment, including even those who have heretofore been defined as especially vulnerable to abuse. To tell a prisoner at Sing Sing that the only available medical treatment is experimental, and that he cannot for his own good participate, adds a loss of medical benefits to the consequences of criminal conviction (Dubler and Sidel 1989).

AIDS advocates also want the FDA to be proactive, not reactive (AIDS Coalition To Unleash Power [ACT UP] 1989). In some ways, this demand requires the greatest transformation in the institutions of drug control. The structure of drug review, for the many reasons we have explored, is heavily biased in favor of caution, preserving all evaluative options until a drug company has provided fully satisfactory data. The critics, however, do not want the government to be so passive; they believe that in an epidemic it is obliged to search out any and all possible therapies, and, if necessary, to sponsor trials itself to determine a therapy's effectiveness and then publicize the results widely. The government's role should be to maximize choice, in the process providing the consumers with the information necessary to guide their decisions, not usurping their right to make decisions. In particular, the government may not use its special control over access to experimental therapies to require people to take part in placebo-controlled studies, or to limit their ability to mix and match therapies (AIDS Coalition To Unleash Power [ACT UP] 1989). The immediate interests of today's patients must come before the more-abstract and long-term interests of science and even those of future patients.

It is most intriguing that the root point of the argument, its rejection of paternalism, fits so perfectly with the pharmaceutical industry's complaints about the drug review process. For the *Wall Street Journal* and similar champions of the desire of business for deregulation, the failure of conventional medicine to offer any therapeutic hope for

AIDS should be blamed on the politics and economics of the drug review process. As they see it, the AIDS shortfall is just another example of "drug lag." Rescind the Kefauver amendment requiring the FDA to measure drug efficacy, declared an editorial in the *Wall Street Journal* in July 1988, and "this single step would help AIDS patients more than any other measure currently being discussed. . . . In the midst of a medical crisis such as this, where does it say in the Hippocratic oath that patients have to accept a 1962 FDA efficacy rule . . . (based on a sedative [thalidomide] given to pregnant women) that forces half of them in these trials to accept a placebo?" (*Wall Street Journal* 1988a). The *Wall Street Journal* reiterated the theme a few months later. Taking note of AIDS advocates' recent protest against the FDA (lying on the ground outside its headquarters with hand-painted tombstones reading "I died for the Sins of the FDA," and "I got the Placebo"), the editorial, not usually supportive of such direct and theatrical street action, declared: "It has become a battle between people who have all the time in the world and people who have little time left in their lives" (*Wall Street Journal* 1989b, 1989c).

In fact, large parts of the AIDS advocates' critique of the FDA could have been scripted by the Pharmaceutical Manufacturers Association. Government must act faster, tell manufacturers precisely what it wants to know, and let consumers and their physicians decide what risks they want to run. Do not worry so much about a few injuries. Do not dally to conduct more tests on animals. When death is the alternative, get on with the job of finding good therapies. All the anger of the gay community and their ability to attract media coverage of their plight—certain to die, to die young, and with no therapies planned—serves as a lever to make palpable what is too often overlooked in the politics of drug review, namely how powerfully injured are those to whom medicine can say only "Sorry, but we know not what to do." There is, to be sure, an incredible irony in all this. Sick gay men, abandoned by a president who refused publicly to acknowledge their disease on all but one occasion, provided the shock troops to move forward his administration's deregulatory drug control program.

While part of the AIDS critique fits perfectly well with the deregulatory plan, a large part of it does not, and the tension between the two visions is most apparent in the approaches to the randomized clinical trial. Many in the AIDS activist community reject the hegemony of scientific controls. To a much greater extent than other groups repre-

senting the victims of particular diseases, where the representation is predominantly by non-ill third parties and the group tends to become so closely allied with investigators and physicians that it functions as an interest group pressing for research funds for the medical establishment, HIV has produced critics who are not linked to medicine. For them, the system of testing should not deny individuals the right to choose their own therapeutic options simply because scientists need controls in order to determine by their own canons of evidence what works best. This is the most basic autonomy claim that consumers advance. But it leaves unanswered the critical question of how one will ever be able to know what does or does not work if there is no system to hold therapies off the market until they are tested in trials.

This then is the dilemma that has shaped the debate around drug regulation and HIV disease. Is it possible to be both proactive and protective, to facilitate medical consumerism while simultaneously guarding against the sale of snake oil, to permit people to choose for themselves while at the same time retaining the capacity to deliver, sooner or later, definitive pronouncements of what works?

The FDA's Response

Let us examine three policies—two announced by the FDA, the third a mix of FDA pronouncements and legislation—in an effort to gauge the ways in which the critique is now shaping law: first, the new rules for marketing investigational drugs; second, the thrust to make the FDA proactive; and third, the FDA's new import policy on drugs. There is an ongoing and extraordinary effort to balance conflicting demands, but whether it will be sufficient to the crisis and produce a stable and workable policy is not at all certain.

Marketing Investigational Drugs

The FDCA prohibits shipping drugs unless an NDA has been approved. The law exempts from this prohibition the shipment of drugs that are intended "solely for investigational use by experts." Complex regulations define the parameters of this exception, and detail how a sponsor gets an "IND," that is, a permit to try investigational drugs. They also spell out the three stages: phase 1 (safety), phase 2 (efficacy),

and phase 3 (clinical trials) through which new testing ordinarily proceeds (Kessler 1989).⁷ In this process, sponsors have enormous responsibilities of data collection and physicians who prescribe investigational drugs are legally and contractually restricted in their use of them, bound to adhere to protocols and to report adverse effects. Ordinarily, investigational drugs are supplied free of charge to physician investigators, and through them to patients. The rationale is that these experiments are part of the sponsor's costs in proving that a drug should be allowed on the market.

In May 1987 the FDA issued rules that permit the sale of investigational drugs for serious or life-threatening diseases. Because these drugs are still undergoing testing, or data analysis concerning them remains to be done, they are, by definition, of uncertain safety and efficacy (*Federal Register* 1987).⁸ To be sure, experimental drugs have been used for therapy before, particularly through so-called "compassionate use" procedures. For example, drugs to correct severe cardiac arrhythmias were made widely available through this mechanism before the FDA authorized full-scale marketing. Nevertheless, the new regime represents a formalization of authority and an encouragement to get drugs in use before their evaluation is complete.

The new regulations are complex in their attempt to balance the desirability of giving very sick patients faster access to promising therapies with the need to pursue the time-consuming and costly process of drug evaluation. To the latter end, the rules limit the investigational drugs to certain diseases, limit the distribution to certain physicians, and have a number of provisions that seek to protect the clinical trial process. They even limit the amounts that companies may charge for the investigational drugs, thereby trying to provide further incentives to complete the quest for full marketing approval. Whether these stipulations can maintain the balance between greater availability and adequate testing is far from certain. As we noted earlier, ideology and symbolism weigh heavily, and the tilt now is toward permitting patients and physicians to reach their own calculus of risks and benefits.

According to the new rules, in order to qualify for treatment status, the drug must be one that treats a "serious" or "immediately life-threatening" disease, and the regulatory commentary promises a flexible ap-

⁷21 *Code of Federal Regulations* 312.21 (1988).

⁸21 *Code of Federal Regulations* 312.7(d) (1988).

proach to defining these terms. In the regulation itself, "immediately life threatening" is defined as diseases where there is a "reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment" (*Federal Register* 1987).⁹ The phrasing "premature death without early treatment" seems broad, and the regulatory commentary indicates that drugs that keep HIV from progressing to clinical AIDS can qualify as directed to a condition that is immediately life threatening. Inasmuch as HIV has a median latency of ten years, this seems to be a major lever by which to spread the language's reach. Moreover, the regulations do not define what constitutes a serious disease. Who will dare to label another's illness trivial? Remember the adage that minor surgery is surgery performed on someone else? It seems unlikely that any bureaucrat will relish the prospect of being called to a hostile congressional hearing to explain just why some class of sick patients is thought to suffer a disease that is not "serious." In other words, the regulations seem bounded in the class of diseases they address, but the potential for expansion, so that patients can choose faster access with higher risks no matter what the disease, is apparent.

The regulations seem to create another barrier, however. This new drug-approval route is only available to treat diseases for which no comparable or satisfactory alternative drug or other therapy exists (*Federal Register* 1987).¹⁰ But here, too, a concept that sounds confining turns out to be much less so on closer examination. Why would a physician prescribe or a patient want to follow an experimental therapy if established treatment works? In fact, justifying experiments with new drugs when existing drugs are satisfactory is a constant issue when alternative drugs are evaluated in sick patients. The regulatory commentary makes clear that the requirement of no adequate therapy will be construed flexibly to recognize, for example, that even where approved treatments are available for a stage of a disease, not all patients respond to them. For these patients, the disease would be "serious," and inasmuch as no satisfactory treatment exists for them investigational drug use would be appropriate (*Federal Register* 1987).

The key question about the scope of the May 1987 regulations is the standard the FDA will use in deciding whether or not to permit treatment use of an investigational drug. The new criterion for approving

⁹21 *Code of Federal Regulations* 312.34(b)(3)(ii) (1988).

¹⁰21 *Code of Federal Regulations* 312.34(b)(ii) (1988).

this use for a drug directed to an immediately life-threatening disease is highly permissive: the commissioner must permit the drug to be marketed unless the scientific evidence, taken as a whole, fails to provide a reasonable basis for concluding that the drug "may be effective" or, alternatively, demonstrates that it would expose the patient to "unreasonable and significant additional risk of illness or injury" (*Federal Register* 1987).¹¹ Hence, when a drug is not particularly toxic, all that is required is some "scientific" evidence pointing toward possible efficacy. Although sheer theory will not suffice, a standard of "may be effective" precludes only those treatments for which a physician might be guilty of malpractice for recommending them. If there are some promising test results, with no sign of major toxicity, the commissioner has no legal right to restrain marketing. By contrast, the commissioner may deny treatment use of a drug intended to treat a "serious" disease if there is insufficient evidence of safety and effectiveness to support such use. This legal standard imposes no control on agency discretion.

If the investigational drug is approved for treatment use, it may then be prescribed by physicians who have been specially designated and recruited for this purpose. Like physicians who test new drugs generally, they must agree strictly to limit the conditions for which the drug is prescribed. Similarly, they must keep records and report adverse drug reactions to the FDA. It is not clear what other conditions may or must be imposed on the physician-selection process. While the statute assumes that only some physicians are "specially qualified" to evaluate investigational drugs, the regulations give no hint that ordinary community physicians lack the relevant skills. Yet, the regulations contemplate using local IRBs to approve patient participation in investigational therapies. Most physicians, however, may not be associated with institutions that have IRBs. Moreover, what will it do to a manufacturer's relationship with physicians if it refuses to treat them as qualified? (*Federal Register* 1987).

The manufacturer's prize under the new regulations is the right to sell the drugs. To be sure, this right is not the right to commercialize the drug: it may not be advertised or promoted.¹² But again, a stipulation that seems restrictive turns out to be quite relaxed. Advertising

¹¹21 *Code of Federal Regulations* 312.42(b)(ii)(E)(1) and (2) (1988).

¹²21 *Code of Federal Regulations* 312.7(d)(3) (1988).

may be insignificant if informed patient groups are prepared instantly to publicize any possible therapeutic advance and, as we shall see shortly, the government itself is pledged to keep consumers informed about potential AIDS therapies. The price that may be charged for the drug is not what the traffic will bear but rather a price limited to what will cover costs of research, production, and distribution. As a practical matter, however, the costs of research and small-scale drug production are so large that this restraint on price seems illusory. Similarly, the principle that charging for an investigational drug permits the FDA to inspect accounting records (*Federal Register* 1987) may deter some drug companies from charging. Similarly, fears of increased product-liability exposure, and a sense of what makes for good public relations may lead firms to give away what they could sell. For small biotechnology companies, where access to the market is everything and every nickel of product sales helps, one may find a marked readiness to use this track.

Perhaps a greater barrier than government limits on drug pricing will be the readiness of third-party payers to reimburse those who purchase the drug. For a number of years, the FDA's stringent requirements on proof of new drug efficacy have served as a shield by which third-party payers have resisted payment for experimental therapies. Now that the FDA is releasing drugs earlier, but without any final assertion of safety and efficacy, third-party payers face the issue of whether they should reimburse for what is still, technically, a part of the experimental process. The third-party payers obviously are on the horns of a difficult dilemma, and several so far, under pressure from advocacy groups, have agreed to reimburse before such time as the drug is finally approved.

Finally, the new regulations contemplate that these investigational drug uses, with the exceptions we have noted, still must fit in under the older approval system. The new track coexists with the traditional one. Thus, the rules strongly caution that approval for this new procedure will be limited to drugs that are at the same time undergoing controlled clinical trials and whose sponsors are actively pursuing full marketing approval with due diligence (*Federal Register* 1987). It is this concern with the on-going clinical trial process that points up the most difficult aspect of the rules. How will it be possible to maintain the clinical trial process if the drug can be obtained without the rigors of being submitted to controlled, and often placebo-controlled, trials? Where will the patients come from to join the clinical trials when the investigational drug is already available for purchase? One possible an-

swer is from the poor, with the prospect that we will return to the days of ward medicine; in its updated version, the well-to-do will have early access to promising therapy while the poor, because they cannot afford to pay, will be left to join the clinical trials. On the other hand, conscience may intervene in the form of an insurance provision to cover the expenses for the poor; but then the clinical trial process may well languish for want of adequate enrollments. If that occurs for an investigational treatment drug, will the FDA remove from the market a drug that clinicians report enthusiastically to be working? It seems highly improbable, even though the failure to do so will undercut the prospect of ever learning about a drug's efficacy through a randomized clinical trial.

However novel the May 1987 FDA regulations are, it should be clear, first, that they are not the lead paragraph in the obituary of the FDA. Although implementation will be affected by how the various parties respond—from pharmaceutical manufacturers to patient interest groups, from doctors to Congress and the courts—an agency that can throw a foreign nation into chaos over two tampered grapes plainly has the power to administer its rules to accomplish what it defines as necessary for public safety. The regulations are not so tightly worded as to stop them.

Second, the May 1987 rules do not explicitly incorporate a patients' rights model. Whether or not a drug gets treatment status is the decision a sponsor, almost always the manufacturer, must make. If the manufacturer chooses not to seek it, preferring, for example, not to open its books to FDA audit or to jeopardize its recruitment of subjects to a randomized clinical trial, or to render itself liable to malpractice suits because the drug turns out to be more toxic or less effective than it seemed, there is nothing that a patient seeking access to treatment can do. While a physician may seek to sponsor such treatment status, the manufacturer's readiness to go along almost always will be necessary.

Third, once the drug is on the market through the treatment exception, it is possible that the FDA will no longer feel intense pressure to approve the drug for full marketing and will, therefore, stretch out the investigational process endlessly. If that happens, the result of the regulatory innovation might well contradict the original impulse. Instead of speeding up approvals and marketing of new drugs, it will have served to increase delays.

But despite these qualifications, the potential impact of the new

regulations is considerable and may well be advancing a new model of consumer rights. In particular, the standard for approving a treatment use of an investigational drug looks to patients' right to calculate their own risks by promising access if there is evidence that a drug may be effective. It is the patient and the physician, not the FDA, that will be making a critical judgment about what drugs should or should not be taken in a war against a disease.

Toward a Proactive FDA

In October 1988 the FDA issued a second set of regulations, the so-called subpart E regulations, designed to facilitate faster evaluation of products directed to "life-threatening" and "severely debilitating" diseases. These regulations build on the ideas incorporated in the May 1987 treatment IND regulations, and commit the FDA to assisting sponsors in designing research. Subsequently, the Congress with the AIDS amendments of 1988 has committed the FDA still further to a facilitative approach to drug development. Increasingly, the government will take on the task of deciding what drugs get tested and how.

The central thrust of the October 1988 regulations is to involve the FDA in clinical trial planning, with the thought that better planning leads to shorter trials (*Federal Register* 1988). If drug sponsors are contemplating testing products that treat life-threatening illnesses or severely debilitating illnesses, the sponsor may request to meet with FDA reviewing officials early in the drug-development process to review and reach agreement on the design of necessary clinical and preclinical studies. To the extent that the products are directed to conditions with clear clinical endpoints, such as death, it should be possible to plan trials that reveal quickly whether the drug is effective. The importance of this innovation is that by involving the FDA in the very process of clinical study design, it puts an end to the adversarial posture. Studies that the FDA regards as inappropriate measures of clinical efficacy and safety will now be avoided. The potential risk of FDA involvement, however, is that by issuing a formal agreement about what must be done in order to prove a drug's worth, the FDA will find it much more difficult to rethink positions taken early on, even though it may discover important considerations that it missed earlier.

The new proposals do recognize that faster review will inevitably leave many potential problems unresolved, and, therefore, they incor-

porate a subtle shift in the standards for approving drugs. Thus, the 1962 statute required that drugs be proved safe and effective. But now, for products treating life-threatening or debilitating illnesses, the FDA proposes to implement this standard through a "medical risk-benefit" approach. In effect, the FDA will permit the marketing of drugs whose safety parameters are still unknown, if the benefits look substantial. It will then seek to ascertain the answers about the precise range of treatment effects and dangers while the drug is on the market. Yet, unlike the situation with the 1987 treatment INDs, where only physicians who agree to act as investigators and live by the reporting rules may have access to the drug, under these new regulations the drug is actually on the market. Any physician is free to use it for whatever purpose, subject only to the discipline of potential malpractice liability and perhaps the refusal of third-party payers to reimburse nonindicated uses. Again, the central issue is the feasibility of a two-track system, continuing closely controlled investigations while permitting general use.

Two other aspects of the October 1988 regulations warrant brief mention. First, the FDA proposes to make its 1987 treatment provisions applicable to drugs that are fast-tracked in this manner. Thus, a drug might be made available for sale if promising data appear in early phase 2 studies, so that data from perhaps as few as 200 patients will suffice to get a drug on the market and earn its sponsor money. Second, the FDA has indicated in these regulations that it is itself prepared to carry out some of the critical testing as part of a regulatory research program. For example, the FDA may do the work to develop assays or determine necessary manufacturing standards. Here, too, the changes promise to reduce the expenses of drug innovation.

These rules are potentially of enormous benefit to the United States biotechnology industry, long filled with promise but short on products. To a greater extent than conventional pharmaceuticals, the new biotechnology products are based on an understanding of disease processes at the molecular level and in genetically engineering products to respond. Successes are more likely, if they come at all, to be demonstrable with small sample sizes. The new rules have the potential to reduce dramatically the costs of reaching the market by, in effect, eliminating the entire process of phase 3 clinical trials, the most expensive part of the clinical testing process. By getting money back faster, small biotechnology companies have a greater chance of holding on to their own products, rather than having to license them to more established companies.

Congress appears fully supportive of the innovations we have outlined. Indeed, in the AIDS amendments of 1988, it went beyond the FDA in the extent to which it gave legislative support to a consumer-rights approach to drug development. The 1988 law requires the establishment of an AIDS Clinical Research Review Committee within the National Institute of Allergy and Infectious Disease.¹³ The committee must be composed of physicians whose clinical practice includes a "significant number" of AIDS patients. It has affirmative obligations to advise on research on drugs that might prove effective in treating HIV. The committee is to recommend to the secretary of the Department of Health and Human Services new drugs for which preliminary evidence indicates effectiveness in treatment or prevention of HIV, and the secretary is to publish that fact in the *Federal Register* and encourage an application for investigational use. Having done so, the law also directs the secretary to encourage the sponsor to seek a treatment IND so that the drug will be available, and if the sponsor does not do it, it authorizes the secretary to encourage physicians to become sponsors of treatment INDs on their own.¹⁴ Perhaps even more important, the law mandates the creation of a data bank on controlled clinical trials which persons with AIDS can have access to, and it even obliges the government to test whatever underground drugs the community, in fact, is using.¹⁵ Thus, the initiation and control of drug testing is moving from the experts to the community, and the community is to be kept constantly apprised of each nuance of development—the better to be able to secure access to therapy without undergoing placebo-controlled trials.

The Import Policy

The greatest concession to consumer entitlement is the recently announced policy of the FDA permitting importation of drugs for personal use. Unlike the other policies we have considered, this one is not embodied in statute or regulatory language but results from a proclamation of the commissioner concerning the ways in which the enforcement authority of the FDA would be exercised in the future (U.S.

¹³42 U.S. Code Annotated sect. 300cc-3 (West Supp. 1989).

¹⁴42 U.S. Code Annotated sect. 300cc-12 (West Supp. 1989).

¹⁵42 U.S. Code Annotated sect. 300cc-16 (West Supp. 1989).

Department of Health and Human Services 1988). In essence, the FDA has announced that anyone can have access to any drug in the world so long as a physician agrees to supervise its use.

As the recent experience with Chilean grapes makes clear, the FDA has broad authority to exclude from the United States products that do not comply with United States requirements. In the past, the FDA had exercised that authority vigorously to keep out, among other things, laetrile, when groups had organized to procure it in Mexico and distribute it to cancer victims in the United States. The power to exclude an unproven drug intended for the terminally ill was confirmed by the Supreme Court in *United States v. Rutherford* in 1979.¹⁶

Nonetheless, at a 1988 National Lesbian and Gay Health Conference and AIDS Forum, the commissioner of the FDA presented a new policy on imports of drugs. Any person, not only those with AIDS, may import drugs if the product is intended for personal use; if the product is not for commercial distribution and the amount of the product is not excessive (a three-month supply); and if the intended use of the product is appropriately identified and the patient seeking to import the product provides the name and address of a supervising licensed United States physician. If these conditions are met, the individual may not only bring the drugs across the border himself, but may use the mails as well.

The policy represents a striking departure from the FDA's prior insistence on its legal duty to enforce the prohibitions on introducing unproven drugs into United States commerce. Still, it is easy enough to understand the extraordinary pressure the FDA was under. Unlike the cancer situation, where there are many plausible treatments for most cancer patients, there are only a handful of approved treatments to recommend for AIDS. Moreover, as a practical matter, the nation cannot police its borders to prevent determined AIDS activists from simply traveling abroad and returning with drugs whose shipment is permitted in foreign countries but forbidden here. (The failure to keep out heroin and cocaine is surely a lesson in point.) Although the announced policy amounts to a surrender by the FDA of its role as protector of consumer health by certification of drug safety, at least it has

¹⁶42 U.S. 544 (1979).

the virtue of requiring some physician involvement, and it provides a basis for policing to some extent the worst kinds of health fraud. Thus, when a Canadian company announced its intention to lower its price of dextran sulfate and facilitate mail orders to the United States, the FDA moved immediately to block it on the grounds that the company's activities amounted to improper commercial promotion (Boffey 1989).

While the FDA's approach may represent a pragmatic accommodation, the symbolic implications of the move are striking. People are permitted to shop for therapy worldwide, and make their own determinations about whether the risks of treatment are outweighed by potential benefits. The elaborate procedures of American law for protecting against inappropriate risk taking, including IRBs and informed consent requirements, are entirely lacking. To be sure, if a foreign drug looks like it is killing people, the word will get around soon enough, and the government will no doubt be active in spreading the word. But this is government as editor of *Consumer Reports*, not as the protector of sick people from exploitation. Moreover, the import policy is not restricted to AIDS but applies to any medical consumer, at least to anyone who has the resources to go abroad in order to receive treatment there first.

In the long run, easy toleration of imports may play havoc with other aspects of the United States pharmaceutical industry. One of the consequences of the FDA's change in policies, and faster grants of permission to market drugs, is that third-party payers will be increasingly reticent at paying for expensive treatments simply because the FDA has allowed them on the market, without a finding of safety and efficacy. These new therapies will often be very expensive, especially those that have been produced by the new genetic engineering technologies. Will the economic returns that the developers of these therapies hoped for be undercut by imports of similar drugs produced abroad at lesser prices? Finally, progress in treating AIDS is likely to come incrementally and, like cancer treatments, be built on careful combinations of drug regimens to produce maximum destruction of infected cells with as little damage to healthy ones as possible. For these purposes especially, although the point is generally true about clinical trials, it is important to limit the compounds the experimental subject is taking. If experimental subjects have access to a wide variety of alternative therapies, and use them either to augment the effect or protect against the failure of the medications they are receiving in controlled trials, then

the sample sizes of clinical tests will have to get bigger in order to account for the variability that these unauthorized remedies induce. This will undercut, however, the entire thrust of the movement to run smaller but better-designed trials to get the drugs on the market faster. In this same fashion, to the extent that new drugs appear on some foreign markets faster than they do in the United States, the availability of compounds abroad constantly undercuts the incentives to participate in placebo-controlled clinical trials.

Parallel Tracking

The pressure on federal bodies to speed up the distribution of investigational drugs is so intense that proposals are now being offered and endorsed without prior attention to substance or procedure. The most vivid example of this process at work is the "parallel track." First suggested by the director of the National Institute of Allergy and Infectious Disease, and quickly backed by the director of the FDA, the purported purpose is to make available to patients drugs that have moved through phase 1 tests and are about to enter phase 2, that is, drugs that have been demonstrated safe with some prospect of efficacy. Ostensibly, the parallel track is an improvement on treatment INDs, for new drugs would be distributed to community physicians on the basis of findings still more preliminary than early returns from phase 2 trials.

The number of questions left unanswered by the parallel track proposal is quite extraordinary. They range from the kind of data that would merit enrolling a drug in the parallel track to the criteria that would allow patients to receive this drug, and on to the kind of data that physicians (whoever they may turn out to be) ought to be collecting about the effects of the drug. Some proponents, for example, wish to divorce this track from all evaluative mechanisms, on the ground that any effort at data collection will inevitably corrupt the program and diminish its treatment orientation. Moreover, how the parallel track system would interface with the treatment INDs, and with the licensure requirements of the FDA is altogether unclear. And it is difficult at this juncture to describe the interface of the parallel track with the institutional review boards save to suggest that the parallel track will probably attempt to avoid their oversight.

All of the objections that have been mounted against the treatment INDs are still more relevant to the parallel track. If the drug is available simultaneously with the start of phase 2 testing, how will subjects be recruited for trials? Nor is there any agreement on what manufacturers can charge for the drugs, and whether insurance companies would be obliged to reimburse for the drugs. Even more important, the parallel track would seem to compel drug manufacturers to gear up to produce large quantities of a product whose efficacy is only minimally established; should the phase 2 trials prove that efficacy is minimal or less than that of alternative drugs, the companies would suffer major financial losses, to say nothing of the potential for law suits from consumers. If drug manufacturers have been reluctant to use the treatment INDs, there is every reason to expect that they will stay further away from parallel tracks.

However difficult these questions, there remains a still more basic one: What is at the core of the difference between the treatment IND and the parallel track? Apparently, the parallel track will get the drug out to market immediately after phase 1 when there is evidence (to what standard is unclear) of efficacy. The treatment IND was intended also to get drugs out to patients after an early showing of efficacy—so that, if there is any distinction at all between the two, it must be that the standard for the parallel track is even more relaxed to the point where a drug need only demonstrate scant? minimal? any? efficacy. It is just possible that the first proponents of the parallel track did not fully understand the treatment IND rules, that they issued a remedy and are now looking for a problem. The alternative is that the standard of efficacy has been diluted to the point of being unrecognizable.

However difficult it is to describe the design and outcomes of parallel tracks, one element is clear: the path that the FDA has begun to travel and that we have traced here, from the treatment IND to the parallel tracks, all make apparent that the AIDS activists have succeeded in doing what earlier critics of the FDA were unable to do, taking decisions of risks and benefits out of the hands of FDA staff and putting them into the hands of the patients, and nonresearch establishment physicians. The director of the FDA now declares that "the more desperate a disease, the more willing we are to trade on safety and efficacy," which really means that now patients, not the FDA, will be calculating the odds and reaching their own findings.

Conclusion

What, then, should we expect of drug regulation in the future? Clearly, the FDA has been engaged in an exquisite balancing act, attempting to respond to the AIDS-related criticisms without abandoning what it considers to be fundamental principles of good medical science. Can this balance hold? The history that we have been tracing suggests that the tilt is, and will be, to a consumer-rights orientation. Perhaps the events of the past two years represent a strategic retreat on the part of the FDA that will ward off a more total defeat, but it is highly unlikely that the FDA will soon again enjoy the authority that it possessed in the 1960s and 1970s.

There is good reason to anticipate that we will witness increased innovation and less concern for risks in drug development and human experimentation. The nightmare cases have changed; thalidomide and Willowbrook are no longer the ruling images. The number of new drugs for AIDS coming onto the market will increase, and if many turn out to be ineffective, some may accomplish a degree of good. The losses will be forgotten in light of the victories, even if they are slim.

Events that transform policy in the realm of AIDS will not be limited to AIDS. As consumer-rights notions advance in this one disease, they will be (indeed they are already) picked up by other similarly situated groups and their advocates, whether afflicted by Alzheimer's disease or Parkinson's disease. If these groups were originally too "doctor-oriented" to lead the change, they are not so "doctor-oriented" to stand out against the change. Indeed, the FDA in both its May 1987 regulations and its 1988 importation policy is framing its response to look beyond AIDS to other diseases. Hence, we have every reason to expect that the ranks of advocates for opening up procedures will be expanding, coming to include not only those who have long wanted to see deregulation affect federal policy (Reagan's supporters and proponents of a drug-lag thesis) but a variety of patient groups who find themselves victims of disease with no readily effective treatment. In essence, the consumer movement will be contagious, making it all the more likely to spread and to be successful.

The lock of the university investigator on clinical trials will not be maintained. The incentives to other physicians to enter into the process will be high, and they will inevitably come from a variety of backgrounds and be affiliated with a variety of types of institutions. The

tertiary medical center locus for trials will weaken and along with it the singular dominance of the randomized clinical trial as necessary and sufficient "proof."

However staunch the FDA defense of its prerogatives, the concessions that it has already made—and will have to continue to make—will mean that consumers and their doctors will be forced to make difficult decisions without substantial information at hand. There is bound to be more guess work, more hunches, more variety, ultimately more "schools" of medicine—reminiscent of but never quite duplicating the array of schools that characterized American medicine in the nineteenth century. It will be less feasible to define orthodoxy, more impossible for the patient—and for the physician as well—to cite unimpeachable authority. It will be much easier to establish patient self-help groups. *Consumer Reports* is likely to have many analogues in medicine.

Biotechnology firms will flourish, able to reach markets more quickly and, therefore, able to command capital more easily. They will have to withstand the pressures from imported drugs, but they may well be able to compete more effectively with them. Indeed, we might even witness a proliferation of drug researchers, and some successes with a few patients may well be a road to incorporation and financial windfalls. To be sure, the incentives to fraud will increase (if it only takes a sample of 100 patients to get access to the market, how tempting it will be to manipulate the recruitment of subjects and resulting data) and, all the while, knowing what is or is not fraudulent will be that much more difficult.

How far the example set in drugs will spread to other products is not easy to estimate, but it would not be astonishing were product-liability laws weakened (with the drug case raised as the precedent). Let the buyer beware may well be the credo of the future.

Medical insurance companies and other third-party payers will face the most acute dilemmas in deciding what therapies deserve reimbursement. They will have strong incentives to become more conservative—not underwriting every drug that hits the market, especially in light of how costly the drugs will be. But their reluctance will generate counter pressures, and even regulation compelling them to underwrite "unproven" therapies. The rates they charge are bound to increase, thereby giving more fuel to the fire of a national health insurance scheme. Of course, national health insurance costs would also mount, but not so

precipitously as to make it seem absurd to spread the cost of insurance more broadly through some type of national system.

Finally, and with near certainty, the pendulum will swing again: The accumulation of failures will slowly affect public policy. Another thalidomide or Willowbrook scandal will eventually resume its hold on the public imagination, and the FDA will assume more of its older authority. Protection will gain in favor, the enthusiasm for innovation at all costs will wane, and the cycle will begin all over again.

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Appendix Note

We are well aware that the constituent groups that advocate on behalf of persons with AIDS are diverse and often disagree on policy questions. The AIDS "community," like other communities, can and does divide on a variety of issues, including the ones we are analyzing here. (The propriety of running underground and unofficial drug trials is a case in point.) But our goal here is to analyze the general consensus that unites most advocates and hence our use, relatively undifferentiated, of the term "advocates for persons with AIDS," and "AIDS advocates and activists."