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Drug Approval And AIDS: Benefits For The Elderly
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The crisis of human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) has transformed patient attitudes and regulatory practices toward experimental drugs, and this transformation is certain to spread from AIDS to other disease entities. Looking back through the 1960s and 1970s, the fundamental principles guiding consumers and regulators toward unproved therapies reflected a deep caution and suspicion toward drug manufacturers and biomedical researchers. It appeared as though the greed of the one and the ambition of the other were so likely to produce abuses 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 most notable case in point was the thalidomide incident. The drug, widely prescribed in Europe, was in the process of being evaluated by the U.S. Food and Drug Administration (FDA) in the early 1960s, when one official, Frances Kelsey, concerned by reports of peripheral neuropathy associated with thalidomide use, delayed its approval. In the interim, the link between thalidomide and birth defects (typically, warped limbs) became apparent. Although a major catastrophe had been averted, some 3,750 women of child-bearing age (624 of whom were reported as pregnant) had already taken thalidomide on an “experimental” basis. But these “experiments” were mostly an effort of the drug companies to persuade doctors to prescribe the drug. To make matters worse, the precise number of recipients was unknown and their identification incomplete, in large measure because the companies and the cooperating physicians kept very sloppy records. At the same time, exposés involving human experimentation (including the injection of cancer cells into senile patients and hepatitis viruses into the institutional-
ized retarded) made it seem as though researchers would go to any lengths to further their investigations.

**The Evolution Of Drug Approval Policy**

These occurrences stimulated two structural changes of critical importance. First, Congress enlarged FDA's authority to monitor not only the safety but the efficacy of drugs, bringing an unprecedented degree of government oversight to bear on the process of drug evaluation. Second, the U.S. Public Health Service (PHS) issued regulations requiring that all of its funded research involving human experimentation be approved by Institutional Review Boards (IRBs), whose job it was to make certain that the subjects had given informed consent and that the protocols offered greater benefits than risks. Both of these changes presupposed that only close and continuing oversight would protect the consumer/subject from the greed of the drug companies and the ambition of researchers.

In their day-to-day operations, FDA and the IRBs shared a number of premises. For one, they both preferred that protocols follow the "gold standard" of random clinical trials—to FDA, the random clinical trial was the best method for establishing efficacy, and for the IRBs, bad science (which by definition could not yield any benefits) needlessly put human subjects at risk. For another, both presumed that serving as a human subject, even in the best of trials, was a sacrifice; that the role of guinea pig invariably posed dangers; and that those not well situated to define or assert their own self-interest—the mentally disabled, prisoners, and children—should come under heightened regulatory superintendence. For still another, both were comfortable in trading off innovation in favor of safety. Better an effective drug should come to market later than a harmful drug be released. This outlook earned FDA the opprobrium of drug manufacturers and criticism from a number of academic analysts as well, sparking a contentious debate on whether or not the United States was suffering a "drug lag." FDA procedures certainly raised the cost and increased the time necessary to market a drug, to some observers altogether unnecessarily. But insofar as public policy was concerned, whether formulated in FDA’s offices or on Capitol Hill, the judgment was that the need to protect the consumer more than outweighed the cost of a drug lag.2

Thus, through the 1960s and 1970s, at a time when patient autonomy and individual rights were transforming many aspects of medicine and health care delivery, drug testing and regulation remained one area in which paternalism flourished. FDA and the IRBs decided for patients whether a new drug was safe enough to be used in clinical trials. Consum-
ers had won the right to learn the truth about a diagnosis from their physicians and to refuse treatment, but in the arena of drugs, it was the experts who continued to make the critical decisions.

**The Challenge To The Drug Control Model**

People with AIDS and their advocates (despite a number of significant differences among them) challenged each one of these principles and by now, to an astonishing degree, have undercut them. Confronting a deadly disease with no known cure, the AIDS advocates rejected the idea that someone else should be deciding what risks are appropriate to take. Moreover, dismayed at what they consider the too-slow pace of research, AIDS activists have organized to track down every therapeutic possibility, wherever it might appear, and to do everything possible to make such drugs available to people with AIDS and HIV infection. All the while, they declare it the right of patients to have unrestricted access to these new experimental therapies, whether or not the therapies have been “proven” through the canons of “good science.” Finally, AIDS activists insist that experimentation is not a burden to be avoided but a form of treatment to be expanded, and persons (including prisoners, for example) should not be deprived of access to experimental protocols. To tell an inmate that the only available medical treatment is experimental and that he or she cannot for his or her own good participate makes a travesty of the principle of paternalism.

AIDS advocates also reject the sanctity of the randomized clinical trial. They contend that individuals should not be denied the right to choose their own therapeutic options because scientists need controls to determine, by their particular canons of evidence, what works best. This claim is the most basic autonomy claim that consumers advance: no one should be required to sacrifice his or her own well-being to advance the claims of science; the counterargument, that the new drug is of unknown efficacy, does not negate the subject’s wish to calculate risks and benefits. These assertions leave unresolved the critical question of how one will ever be able to know what does or does not work if there is no system to keep subjects from obtaining therapies outside of the clinical trial. Will it be possible to accommodate consumer demands and simultaneously guard against the spread of snake oil? Can patients be permitted to make their own choices while the scientific community retains its ability to learn about the effectiveness of new agents?

**Assessment of risk and benefit.** Part of the power of the AIDS critique comes from the facts of the disease: when young men and women face untimely and certain death, there is a strong presumption that they ought
to be able to make their own assessments of risks and benefits. And since the first patients with HIV disease typically were well-educated, middle-class Americans, the notion that they needed the guidance of experts seemed less compelling. But another part of the power of the critique also comes from the fact that it fits ever so well with the antiregulatory stance of the Reagan administration and its supporters. Rescind the Kefauver amendment requiring 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?”4 *The 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 column, 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.”5

**The FDA response.** The FDA response to these challenges has been one of judicious retreat, trying to accommodate the new demands without forsaking altogether its oversight role. Thus, in a striking turnaround, FDA now allows the importation of drugs for personal use. Anyone can have access to any marketed drug so long as a physician agrees to supervise its administration. The reasons for this reversal are not difficult to appreciate. Unlike the case of cancer, where a variety of standard (if only modestly effective) treatments exist, only a handful of approved treatments are available for AIDS. Moreover, as a practical matter, a nation that cannot police its borders to prevent the importation of heroin and cocaine by drug dealers is not going to be able to prevent the importation of compounds by determined AIDS activists. The new FDA policy does, at least officially, require some physician involvement and attempts to minimize the worst kinds of fraud by restricting advertising and commercial distribution.6 But the agency that refused to permit the importation of laetrile to treat cancer is now on the record as saying that consumers are free to import a drug of choice if it is for their own use. If one considers the effect of a police announcement that it will no longer prosecute those who use a small amount of marijuana, one has a sense of the symbolic significance of the new FDA position.

Even more notably, FDA has altered its formal policies on access to investigational drugs. Heretofore, it had refused to license the shipping
and sale of drugs until their safety and efficacy were fully established. When unproven drugs were used for therapy, it was in one of the stages of clinical trials—Phase I (for safety), Phases II and III (for efficacy), or, on occasion, as part of the “compassionate use” exception. In response to AIDS activism, however, FDA has formalized a number of shortcuts to make drugs available sooner and under a broader number of conditions. In May 1987, it approved regulations that permit the sale of investigational drugs for serious or life-threatening diseases through a treatment IND (investigational new drug) procedure. Because these drugs are still undergoing testing or the data are still being evaluated, they are by definition of uncertain safety and efficacy; nevertheless, FDA is permitting their sale and use before evaluation is complete. The qualification that the disease be “serious” or “life-threatening” need not be very restrictive. For one thing, who would dare to label someone else’s illness not serious? For another, the regulation defines “immediately life-threatening” as diseases for which there is a “reasonable likelihood that death will occur within a matter of months or premature death is likely without early treatment.” The regulatory commentary indicates that drugs that keep HIV infection from progressing to clinical AIDS can qualify as directed to a condition that is immediately life-threatening. Inasmuch as HIV infection has a median latency of ten years, this seems to be a major lever by which to spread the language’s reach.

The new FDA regulations insist that these investigational drugs, despite their having been approved for treatment use, must still ultimately prove their worth under conventional evaluations. The new track coexists with the traditional one. Thus the rules strongly caution that approval for this new procedure will be limited to drugs whose sponsors are pursuing controlled clinical trials. This continued commitment to the clinical trial process frames 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 need to submit to the trials? Where will the patients come from to join the trials when the investigational drug is already available for purchase?

This question is no less relevant to the recent policy statement recommending the so-called parallel track for investigational drugs. On its face, this proposal would permit clinical use of investigational drugs prior to the time that FDA would permit their release under a treatment IND. However, the parallel track policy recommends that these drugs be made available only to persons who cannot participate in clinical trials. (It is worth noting that the treatment IND regulations contain no such restriction, although presumably FDA or the drug sponsor might impose it in a particular case.) In sum, when it comes to investigational drugs, the requirements of clinical trials still conflict with the rights of consumers.
Despite an unwillingness to come down firmly on one side or the other, it is apparent that FDA has shifted its posture from one of thoroughgoing paternalism to a greater readiness to allow patients and physicians to make their own calculations of risks. It is no longer the experts who will decide, unilaterally, which risks are worth assuming. Instead, the patient, with help from physicians and other consumers, will be determining which drugs to take or not to take in the war against disease.

**Impact On Diseases Other Than AIDS**

Although these changes have been first advanced by AIDS activists, there is every reason to believe that they will spread beyond the case of AIDS. Indeed, FDA has expressly noted that the treatment IND program is not restricted to AIDS. Thus, other patient groups will soon be attempting to avail themselves of the same prerogatives, including, in particular, the elderly and their families who are affected by the incurable and devastating conditions that Alzheimer’s disease or strokes can inflict.

The exceptionally aggressive and effective agitation of the AIDS coalition reflects the fact that the coalition existed before the disease struck. Carrying a self-definition of a minority, and a stigmatized one at that, and convinced that only a dedicated political campaign would secure its goals, the gay community was already organized and energized before AIDS appeared. When it became necessary to advocate on behalf of people with AIDS, the structure was in place and the know-how secured; the tactics that had once been employed to combat discrimination were now turned to combat the FDA.

Other patient groups had no such prior political history. Members of national cancer or heart associations, for example, rarely knew one another before becoming patients, and they lacked a sense of being an embattled minority. In fact, the patient organizations that existed in the 1960s and 1970s were mainly (although not exclusively) the result of physicians’ initiatives that sought to expand the resources available for research.

The formation of the Alzheimer Disease and Related Disorders Association (ADRDA) exemplifies the process at work. As Patrick Fox has recently explained, the moving force in the formation of ADRDA was physicians, and their target goal was funding for research. The body did incorporate family and community groups whose agenda was more concerned with the delivery of services to patients than with laboratories. But the conflicts between the two agendas remained low, for the physicians were the more powerful element within the organization.

But if these patient groups were originally too “doctor-oriented” to lead the change, they are not so “doctor-oriented” to stand out against
the change. Indeed, FDA is framing its response to go beyond AIDS to other diseases. Hence, there is every reason to expect that the ranks of advocates in favor of relaxing procedures will be expanding 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 also a variety of patient groups who contract diseases that have no effective treatment. In essence, the consumer movement will be contagious, making it all the more likely to be successful.

**Growing voice of patients.** What we are likely to witness is the replication of the AIDS community’s strategy in other patient groups, particularly in groups affected by devastating diseases for which cures remain unknown. In the past, many of the elderly, particularly in nursing homes, have not been especially eager to participate in clinical trials, at least where the drugs under investigation may offer only limited improvements over existing ones. They have found little advantage to serving as research subjects, and at the same time, the nursing home administrators were not eager to assume additional responsibilities—either because of the inconvenience or because of a nervousness (fed by the earlier exposes) about human experimentation in general. However, these attitudes may well change. If the disease is fatal and the standard therapeutic options are ineffective, patients and their families may begin to insist on receiving active agents, avoiding clinical trials and exercising the same degree of discretion as do people with AIDS and HIV infection. We may witness the emergence of patient groups that emulate the information-gathering and -disseminating characteristics of AIDS groups. All these organizations, moving away from their physician founders, may become more consumer oriented, more impatient with formal clinical trials, and more prepared to import their own drugs and to risk the use of drugs whose safety and efficacy are not well established.

Thus, with the elderly as with AIDS patients, we may witness a greater thrust toward innovation and less concern for risks. Considered against the debilitating effects of a stroke or Alzheimer’s disease, it may seem worth the gamble to try a new drug, however uncertain its effects. In this way, the number of new drugs coming onto the market is likely to 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.

**Shifting locus of clinical trials.** There is also a strong likelihood that the hold of university investigators and tertiary care university hospitals on clinical trials will be loosened. The incentives to other physicians to enter into the process will be high, and nursing homes may find themselves the centers for trials. (It is not difficult to imagine a nursing home promoting itself to would-be residents as a facility that has contracts with companies
to test the newest compounds.) Such changes raise acute concerns about both protection of the subject and the rigor of design, but such concerns may not trump the urge to innovate.

The concessions that FDA has already made and will continue to make will also force consumers and their doctors to make difficult decisions without substantial information at hand. Inevitably, there will be more guesswork, more hunches, and more variety. It will be less feasible to define orthodoxy or to cite unimpeachable authority. Consumer Reports is likely to have many analogues in medicine. Also, medical insurance companies and other third-party payers will face difficult dilemmas in deciding which therapies to reimburse. They will have strong incentives to become more conservative—not underwriting every drug—but their reluctance will generate counterpressures among consumers and even regulation compelling it to underwrite “unproven” therapies.

Finally, the pendulum will swing again; as has happened in the past, the accumulation of failures will slowly affect public policy. Another thalidomide scandal will eventually capture the public imagination, and FDA will assume more authority. Protection will gain in favor, the enthusiasm for innovation at all costs will wane, and the cycle will begin all over again.

NOTES
5. “The FDA for Itself,” The Wall Street Journal, 13 October 1988, A22. See also “New Ideas for New Drugs,” editorial, The Wall Street Journal, 28 December 1988, celebrating the fact that “voices in the American medical establishment are saying the time has come to go back to the drawing board. We’ve been calling for a better, faster way of getting new drugs into the hands of patients for some three years” (p. A6).
8. Ibid.