

Cato Institute Policy Analysis No. 72: Compassion vs Control: FDA Investigational-Drug Regulation

May 20, 1986

Dale H. Gieringer

Dale H. Gieringer is a writer and policy analyst affiliated with the Decisions and Ethics Center of Stanford University.

Executive Summary

"The basic problem is, I don't have as much control over what I can do to get well as I want."

--AIDS patient[1]

"I think the FDA should recognize its responsibility for the denial of lifesaving technology."

--Robert Jarvik, developer of the artificial heart[2]

The Regulation of Life and Death

Victims of AIDS and other incurable diseases are denied access to potentially valuable experimental drugs by the U.S. Food and Drug Administration. Under the present law, no new drug or medical device can be sold until it has been approved as safe and effective" by the FDA. New-drug approval is an expensive process that routinely takes years to complete. Unapproved experimental products cannot be given to human subjects except in investigational studies that have been explicitly pre-approved by the FDA through a process known as "application for investigational drug (IND) exemption."

Because FDA policy typically restricts the use of IND drugs to tightly controlled medical experiments, access to investigational products is extremely limited. As of April 1986, only 200-300 of the country's 10,000 known AIDS patients have received investigational AIDS drugs in IND studies. Because AIDS is presently an untreatable and invariably lethal disease, killing 50 percent of its victims within a year of first diagnosis and nearly all in three years, patients have been eager to try new investigational therapies. However, the FDA has insisted that access to AIDS drugs be strictly limited because of their highly experimental nature.

A dozen or so drugs are presently under investigation for treatment of AIDS. Of these, two or three have shown some preliminary signs of efficacy in human subjects, relieving, though not curing, the disease. One promising discovery has been the drug AZT (azidothymidine), which is reported to have improved the immune systems of 15 out of 19 patients in a recent study.[3] AZT is currently being tested in an efficacy study of 200 patients under a 'double blind' protocol, in which half the subjects receive a placebo ("sugar pill"). As in other AIDS studies, only a fraction of those seeking treatment can be accommodated: at Massachusetts General Hospital, only one-twentieth of the applicants for an AZT study could be

accepted.[4] Admission is limited by drug scarcity, medical-safety concerns, and the economic costs and conditions imposed by FDA regulation. The National Cancer Institute has recently announced plans to undertake wider-scale clinical AIDS studies in a few months; however, FDA officials say that the announcement was premature and that it would be "wasteful of resources" to contemplate wider use of any AIDS drugs at present.[5]

Members of the AIDS community have been highly critical of the FDA. "I'm appalled," said one spokesman. "There's not a day that goes by when I don't get ten calls from people who want treatment. They are told to do nothing and wait for the studies to be done." [6] The FDA cautions against expecting too much. "None of these things we have looked at so far have much in the way of efficacy," said one agency official. "To date they've slowed the virus but they don't totally suppress it." [7] But slowing the virus is itself a significant achievement. The salient point, as noted by one AIDS victim, is that "months can make a difference." [8] At present mortality rates, every week means death to another 100-125 AIDS victims. Thus, a mere two-month regulatory delay in the development of an effective AIDS cure could cost 1,000 lives.

The scarcity of investigational drugs has led many AIDS patients to seek treatment in foreign countries. In a highly publicized incident, the late actor Rock Hudson flew to France for the experimental drug HPA-23. Thousands of AIDS victims have gone to Mexico to smuggle back two other drugs, isoprinosine and ribavirin, that may be of value in treating AIDS. Although the importation of unapproved drugs is a violation of federal law, the FDA has permitted small amounts of isoprinosine and ribavirin to be brought into the country for personal use. However, the quantities allowed are so small that patients routinely smuggle back extra amounts for themselves and for friends.[9]

While isoprinosine and ribavirin may be of some value in mitigating or delaying the progress of AIDS, neither seems to offer a cure. Both drugs are relatively non-toxic and have been widely used in other countries for certain viral infections. Ribavirin has been the subject of more than 500 articles in the medical literature as an antiviral. An aerosol-spray form of ribavirin has recently been approved by the FDA for certain infant respiratory infections, but AIDS patients use a capsule form that is available only in foreign countries. Isoprinosine has been studied for over 10 years and is approved in 89 countries. New Zealand has approved it for treatment of AIDS.

In certain circumstances, the FDA may grant "compassionate INDs" for the treatment of patients who have otherwise untreatable conditions. However, compassionate INDs are permitted only on a discretionary basis, in cases where the FDA judges that there is sufficient evidence that a drug's benefits outweigh its risks. In practice, the FDA's interpretation of this policy is not always generous. In March 1985, a Tucson hospital was refused permission by the FDA to install a temporary, experimental artificial heart in a 33-year-old patient dying from heart failure. The hospital was subsequently reprimanded by the FDA for proceeding with the operation anyway in what proved to be a futile last-ditch effort to save the patient's life. The FDA has continued to restrict the use of artificial hearts, limiting them to a small number of patients and ruling out their use in women altogether.

No AIDS drugs are presently available on a compassionate-use basis. At one point, the FDA did approve isoprinosine for compassionate use, but the manufacturer, Newport Pharmaceuticals, chose not to distribute it because of the cost of supplying it under a compassionate-use protocol. Compassionate INDs require special efforts on the part of both manufacturers and physicians, who are required to comply with elaborate record-keeping, paperwork, and test protocols. Manufacturers are required to provide compassionate-use drugs free of charge, though the cost of supplying them can be quite expensive. According to Newport, compassionate-use distribution of isoprinosine would have cost about \$2,000 per patient; in comparison, a year's supply of the drug can be purchased for \$200 in Mexico, where it is sold by a subsidiary of Newport.

Another problem with the FDA's compassionate-use ruling on isoprinosine is that treatment is restricted to AIDS victims, although most observers agree that its greatest potential may be in treating the pre-AIDS

syndrome ARC, a less acute condition that sometimes degenerates into AIDS. Many physicians suspect that a more effective treatment may be to combine isoprinosine with ribavarin.[10] Although the FDA has refused to permit studies to test this treatment,[11] it is widely practiced among patients who have obtained the drugs from Mexico. The results are being monitored by a private San Francisco group, Project Inform, in the hope of detecting possible treatment benefits and hazards.

The FDA has ruled out compassionate use of AIDS drugs on the grounds that it would be premature until their efficacy has been better demonstrated. The FDA has defended itself by pointing out that the drugs' risks are uncertain. "You don't know whether the drug will help you or harm you," explained one agency official. In fact, studies on at least one AIDS drug were terminated following the premature deaths of several subjects. However, many AIDS victims feel that even a slim chance of help is better than no chance at all. In the words of one patient, "I know what the side effects of untreated AIDS are. Based on past experience, there's a 75 percent chance I'll be dead in two years. What's the harm with giving me some hope?"[12]

The FDA has argued that IND regulations are needed to enforce adequate standards in testing. However, the rationale is by no means self-evident, insofar as other forms of non-pharmaceutical medical testing are exempt from regulation. There is no obvious reason why the safety of investigational subjects could not be adequately guaranteed without the FDA, through professional and institutional review boards, informed-consent protocols, and insurance inspections.

It may also be asked why the enforcement of testing standards should require restrictions on patients' freedom of access to investigational products. In the words of one ARC patient, "I'm all for [well-controlled] studies, but they can have their studies and let people make informed decisions about what they want to do with their lives."[13]

The FDA has replied that free access to experimental drugs would slow down drug research because patients would have less incentive to volunteer for the controlled, double-blind studies that the FDA typically requires in order to prove drug efficacy. In double-blind studies, half the subjects receive placebos, and neither patients nor their physicians know whether they are actually receiving the drug. "If you give in to the pressure [to make AIDS drugs available], how are you going to study the drugs?" asked one FDA officer. "Pretty soon you can't do a study [involving placebos] because no one wants one."[14] In requiring that potentially life-saving treatment be withheld in order to obtain subjects for FDA studies, the agency's policy effectively places the burden of efficacy testing on patients, rather than allowing the market to determine the level of testing desired by consumers. The necessity of double-blind studies has been questioned on both scientific and ethical grounds in the case of such life-threatening diseases as AIDS.

To the extent that double-blind studies may still be needed, a basic problem is that experimental volunteers are undercompensated for their participation, usually receiving nothing more than free treatment. One solution would be to offer increased volunteer benefits. Another would be to increase the costs of investigational drugs to patients who did not wish to participate in double-blind studies. A strong economic case can be made for changing the law that requires companies to supply compassionate-use drugs free of charge and for having patients help pay the costs of drug research and development, including compensation for double-blind volunteers.

Toward an Informed-Choice Policy

A fundamental problem with the FDA approval system is that it denies individual choice in risk. Consumers and physicians are not allowed to decide for themselves what drug risks to assume but are forced to abide by whatever the FDA decides. Inherent here is the assumption that safety and efficacy are objective, scientific concepts that can be rationally imposed on a society-wide basis. In fact, drug safety and efficacy are inherently subjective, varying greatly from individual to individual for three basic reasons:

Subjectivity of Values. All decisions on drug safety and efficacy involve human values and attitudes

toward risk.[15] Thus, risks that are acceptable to one patient may not be to another. Some patients are willing to submit to extreme risks for relief from conditions that they find intolerable; others will endure the greatest misery rather than take even the slightest risk of getting worse. By attempting to dictate the level of personal risk, the current approval system violates principles of personal freedom fundamental to a free society.

Diversity of Medical Circumstances. Decisions on the use of drugs vary according to a host of individual variables and circumstances. As pointed out by economist F. A. Hayek, regulators and other central planners are unlikely to have adequate "knowledge of the particular circumstances of time and place" relevant to human decisions.[16] A perverse characteristic of the present FDA approval system is that it often imposes decisions that are harmful to individuals on the supposed grounds of public health.

Uncertainty of Medical Risk. Like all human knowledge, medical knowledge of drug risks and benefits is inherently uncertain. Experts commonly disagree over drug risks and benefits; in the case of AIDs, they express varying opinions about the use of investigational drugs. Any attempt to resolve medical controversy by regulatory fiat is inevitably arbitrary and controversial and is questionable on both ethical and scientific grounds. As long as there are reasonable scientific grounds for debate, it is ethically dubious whether regulatory force is justified in preventing drug use by patients and physicians who are willing to assume the risks. To avoid uncertainty by forbidding potentially risky experiments rules out the likelihood of potential benefits.

A general solution to the drug-regulation problem would be, as some FDA critics have argued in recent years, to allow unapproved investigational products to be freely used and sold along with appropriate information and precautions on risk--an "informed choice" policy.[17] The essential object of the policy would be to inform, but never limit, consumer choice. The present system often discourages informed choice; for example, dangerous prescription drugs are commonly sold without any consumer-warning labels.

Informed consent is an essential prerequisite of human drug use. Difficulties in applying the principle arise mainly in the case of children, the senile, and the mentally incompetent and are generally resolved through accepted principles of legal guardianship. It is sometimes alleged that desperately ill patients are likewise incapable of giving informed consent. Proponents of this view often claim that the desperately ill must therefore be protected by regulation from submitting to dangerous experiments--a view that seems to have few supporters among either the physicians or the patients concerned. AIDS researchers report few problems with informed consent and feel that lawsuits for malpractice are a minor risk. Ethical disagreements over experimental-drug use are inescapable, and there is no evidence that they can be settled through regulatory intervention. Forcible government interference with private, personal decisions raises ethical issues of a different order, however, which can in turn become political issues. The following sections examine the current system of investigational-drug regulation from an informed-choice perspective.

The Historical Background of FDA Regulation

The Prescription-Drug Monopoly

Until 1938, there were no restrictions on access to pharmaceutical drugs aside from narcotics. The only major requirement of federal legislation was that products not be adulterated or misbranded, as specified by the Food and Drug Act of 1906. The Food, Drug and Cosmetic Act of 1938 (FDCA), passed after 107 people were killed by the toxically misformulated drug Elixir Sulfanilamide, required that all new drugs be approved as safe by the FDA before being placed on the market, a procedure known as "new drug application" (NDA) approval. Originally, FDA approval was necessary only for pharmaceutical products, but it was mandated for medical devices by the Medical Devices amendments of 1976.

An important unforeseen consequence of the FDCA was to prohibit over-the-counter sale of prescription

drugs. In interpreting a provision in the FDCA that drugs be labeled with adequate instructions for safe use, the FDA ruled in 1938 that certain drugs were inherently difficult to label in layman's language and might therefore be labeled with the simple warning "Caution: To be used only by or on the prescription of a physician." [18] The FDA also ruled that the sale of such drugs without a prescription would be illegal. Despite the fact that Congress had explicitly disavowed any intent to interfere with the right to self-medication when it passed the FDCA, the 1938 ruling--which established the current prescription-drug system--proved politically uncontroversial. It was popular with physicians, who received the monopoly right to prescribe, and with manufacturers, who were relieved from the burden of extra labeling. The prescription-drug restrictions were formally written into law by Congress in the Humphrey-Durham amendments of 1954.

A perverse consequence of the prescription-drug system was to deprive patients of potentially valuable information on drug usage and risks. Unlike consumers in many foreign countries, Americans do not receive manufacturer labeling with prescription drugs. Although the FDA requires that manufacturers publish technical "package insert" information for physicians, it is typically discarded by the pharmacist before it reaches the patient. The theory is that doctors will provide the appropriate prescription-drug information to their patients themselves; in practice, physicians commonly neglect to provide important drug warnings. According to a recent FDA study, 80 percent of the patients surveyed received no drug information whatever from their physicians. [19] There is ample evidence that prescription-drug misuse and misprescription are widespread problems. [20]

In recent years, many consumer advocates have called for "patient package insert" labeling for prescription drugs. Despite the objections of some doctors that PPIs might scare patients, polls have shown widespread consumer demand for such labeling. [21] In 1979, the FDA proposed requiring PPIs for 10 commonly misused prescription drugs but was overruled by the Reagan administration. Ironically, PPIs were rejected on the grounds of "overregulation," although it is likely that they would long ago have been required by modern product-liability law had FDA regulations not exempted manufacturers from labeling requirements.

The Drug Lag

In the early years of the FDCA, the requirements for new-drug approval were rudimentary and did not greatly affect the rate of drug development. However, approval requirements were drastically tightened in 1962 by the Kefauver-Harris drug amendments, passed after some 10,000 babies were born with severe birth defects to mothers who had taken the tranquilizer thalidomide during pregnancy. Although the United States was spared significant casualties because the FDA had refused to approve the drug, Congress nonetheless acted promptly to strengthen FDA regulation.

The 1962 amendments broadly expanded FDA authority into virtually every aspect of drug research and development. Importantly, the new legislation required that new drugs be proven not only "safe" but also "effective." The result was to ban potentially useful but unproven cures from the market. The efficacy provision was the first major item of FDA legislation opposed by the American Medical Association, which attacked it as a violation of the patient's freedom of choice--a problem the AMA had failed to discern in the prescription-drug system.

The amendments also established the present IND system, which requires FDA approval for all human use of unapproved investigational drugs. Before 1962, the FDCA had prohibited the sale of unapproved drugs without otherwise restricting their use or distribution. Further regulation was urged following the thalidomide disaster, when it was found that the manufacturer had distributed over 2.5 million promotional samples of thalidomide to U.S. physicians. [22]

IND regulation gave the FDA the monopoly authority to determine the standards, conditions, and direction of new-drug development. Subsequent regulations dictated strict animal testing, multiple double-blind studies, detailed and exhaustive record keeping, inspections of laboratories and clinics, and standards for

"good clinical practice" and "good laboratory practice." Ironically, it is doubtful whether the observance of these provisions could have prevented the thalidomide disaster. Most subsequent testing of the tranquilizer in animals, for example, failed to reveal evidence of its dangers.[23]

The years after 1962 witnessed a dramatic increase in the time and cost of new-drug development. From 1955-60 to 1965-70, the average number of new drugs approved by the FDA plummeted from 50 to 17 per year, leading critics to argue that FDA over-regulation was causing a "drug lag," or slowdown in U.S. drug development.[24] As shown in an influential study by William Wardell and Louis Lasagna, drugs were approved months or years sooner abroad than in the United States.[25] In addition, a growing number of "orphan drugs," drugs of unique value to special patients, could not be placed on the market economically because their potential sales were too small to cover the costs of FDA testing.

By the 1970s, the FDA bureaucracy had become notorious for inefficiency, red tape, and delay, with paperwork running into tens of thousands of pages and processing times extending two years and longer. The FDA's procedures were criticized in a Government Accounting Office report entitled FDA Drug Approval--A Lengthy Process That Delays the Availability of Important New Drugs,[26] and economic studies suggested that consumers were being hurt by excessive delay of useful new drugs. In a famous cost-benefit study, Sam Peltzman concluded that the consumer costs of the 1962 amendments had outweighed benefits by about 4 to 1.[27] Critics argued that political pressures inevitably made the FDA systematically too risk-averse because the casualties from new-drug accidents generated more publicity than the invisible casualties of drug lag.

In 1979, Congress held hearings on the drug lag.[28] In response, the FDA initiated internal reforms to provide "fast track" approval for important new drugs. FDA reform gained further momentum under the Reagan administration, which announced deregulatory changes aimed at reducing unnecessary paperwork, reducing duplicate studies, and generally streamlining the approval process.[29] In 1982, Congress passed the Orphan Drug Act, allowing the FDA to make certain drugs eligible for special approval treatment and tax credits.

As a result of these measures, FDA performance has improved considerably. Newer agency personnel are credited with being more responsive and with acting to expedite the approval of important new drugs. Approval times for such drugs have been reduced by about 40 percent, to an average of 19 months. Meanwhile, the number of new drugs approved by the FDA has surged to its highest level since before 1962, reaching 30 in 1985.

However, many of the improvements in the FDA's performance reflect personnel changes and internal policy measures that could easily be reversed under future administrations. Agency performance has been spotty and is recognized as especially poor in device regulation. The FDA has been criticized for failing to keep track of reports of adverse drug reactions and for withdrawing measures for prescription-drug patient labeling.

Importantly, new drugs still take years to reach the market, during which time they are largely inaccessible, and hundreds of foreign drugs remain legally unavailable.[30] After 48 years of agency regulation, there is no scientific evidence that the FDA approval system is on balance beneficial to public health. The cost of a mere one-year delay in new-drug approval can be estimated at as much as 37,000-76,000 lives per decade--several times the worldwide toll of all new-drug accidents.[31] As many as 30,000 lives could be lost from a mere one-month delay in the availability of an effective cure for cancer.

It is dubious how much more can be achieved through FDA regulatory reform without fundamental legislative changes. New-drug approval can be hastened only so much before the risks become unacceptable. In 1982, the FDA was forced to backtrack from deregulatory reform when 11 Americans were killed by the new arthritis drug Orflex, approval of which had been speeded up under the agency's fast-track policy. Despite the fact that some patients appeared to derive unique benefits from the drug and sought to maintain access to it after it was withdrawn from the market, the FDA was widely attacked for

lax regulation.

The Oraflex case illustrates a basic problem in the present approval system, in which drugs can be marketed only if approved as fully "safe and effective" on a once-and-for-all, society-wide basis: as long as patients differ in their individual attitudes toward risk and their physiological responses to drugs, the society-wide approval guarantee will inevitably prove unsatisfactory. Under an informed-choice policy, drugs of different degrees of safety and efficacy would be sold with appropriate warnings. Such new, relatively unproven drugs as Oraflex would be marketed with prominent label and/or oral warnings to beware possible unknown reactions. Consumers who wished to avoid exposure to potentially hazardous medication could do so, while others would be free to assume the risks.

The Regulation of Investigational Drugs

Drug researchers are required to submit IND applications whenever they administer FDA-unapproved drugs to humans. Drugs may be sponsored by manufacturers, academic researchers, and, in the case of compassionate INDs, individual physicians. Additional IND applications must be filed to test an already FDA-approved drug in an unapproved new use or indication. However, there is no law forbidding individual physicians to prescribe approved drugs for unapproved indications, though they are often reluctant to do so.

The FDA insists that drug investigators have appropriate medical credentials. A simple general practitioner, for example, would typically not be allowed to embark on a study of a new cancer drug. Restrictions of this sort are accepted by the medical community to the extent that they may prevent negligence or quackery. However, there are times when they may inhibit the potentially beneficial use of a drug. The artificial heart has been limited to only a handful of surgeons, despite the protestations of its primary developer.[32] Similarly, the distribution of AIDS drugs is currently restricted to a handful of research centers. Patients may find it inconvenient, expensive, or impossible to obtain treatment at an FDA-approved treatment center.

An IND application requires information on the medical credentials of the investigator, the chemical and pharmacological nature of the drug, the design and purpose of the test, and evidence of animal testing. It may vary in length from a couple of pages to 100 or more. The FDA also requires continued monitoring and testing of the drug's effects on the patient. The FDA is generally noted for its zealous insistence on detailed and accurate record keeping; inevitably, much of the requested information is of questionable relevance to a given study.

Bureaucratic obstacles to IND approval were most severe in the 1960s and 1970s. In one famous case, a study of the use of aspirin to prevent heart disease was canceled when the FDA demanded that the sponsor submit with its IND application a survey of the extremely voluminous medical literature on aspirin.[33] Several years later, a similar study was conducted at government expense, and it has finally been verified that aspirin is in fact useful in preventing cardiovascular problems. The number of stories of this kind has decreased somewhat in the wake of recent regulatory reforms. Unlike NDA applications, which usually take many months to process, IND applications are typically processed in 30 days or less. In the case of AIDS drugs, the FDA has made special efforts to pass on INDs in 5 days or less. Compassionate INDs can be granted on the basis of a phone call, though follow-up paperwork is required. The FDA officers in charge of AIDS and cancer drugs have been praised by researchers for their responsiveness in recent years.

Unlike most foreign drug-approval agencies, the FDA exercises the power to inspect the records and premises of any drug investigator. It also promulgates extensive regulations on "good laboratory practices" and "good clinical practices," among which are the requirements that all investigational drugs be kept under lock and key and that all doses be accounted for. Violators can be suspended from medical practice.

The FDA is notably more reluctant than foreign drug agencies to accept experimental data from abroad because of its suspicion of low foreign enforcement standards. It has generally been agency policy to delay

the approval of foreign-approved drugs until additional, domestic studies can be performed. It is questionable whether the risk of accepting foreign data is so great as to justify the cost of delaying new drug introductions accordingly. However, the agency did liberalize its policy in 1982 to approve Oralflex on the basis of British data, only to be embarrassed when Oralflex turned out to be toxic.

The FDA has often manifested a "regulatory imperative," trying to extend its regulatory authority to no apparent benefit. Thus, in 1983, the FDA demanded regulatory compliance from researchers investigating the use of low-power 'cold laser' light for pain relief. The research involved nothing more than shining low-powered laser light on skin and was conceded by one FDA official "not to be harmful at all."^[34] Nevertheless, the FDA reprimanded the researchers for not proceeding with the required investigative-device exemption (IDE, the IND equivalent for medical devices).

Investigational-Drug Approval Policy

Rarely does the FDA actually refuse an IND application altogether. Rather, it frequently imposes additional conditions upon the applicant, such as revisions in experimental design and additional animal studies. The effect can be to prolong and increase the cost of drug studies, if not to prevent them altogether. Theoretically, such costs are economically justifiable to the extent that they result in better knowledge of the drug; however, the FDA does not submit its regulations to cost-benefit analysis. A natural effect of FDA regulation is to implicitly preclude certain kinds of studies from being undertaken or submitted for IND approval in the first place.

On occasion, sponsors have been forced to abandon a drug investigation altogether following the refusal of an IND application, as in the case of the aspirin study mentioned earlier. Another notable instance involved the drug DMSO, an industrial solvent of possible benefit to victims of arthritis, bursitis, sclerodama, muscle sprains and strains, and brain traumas. Permission for human testing of DMSO was effectively revoked by the FDA in 1967 following a series of disputes between agency officials and Stanley Jacob, a principal investigator. The arguments invoked by the FDA to support its position appear to have been medically questionable.^[35] DMSO had been administered to over 50,000 patients, with hardly any adverse reactions, and many patients reported unique pain-relief benefits. Before its testing was halted, DMSO was approved by the FDA for the treatment of a relatively rare condition known as interstitial cystitis and for veterinary treatment of arthritis.

Despite FDA disapproval, many patients continued to use DMSO, which remained legally available on the gray market as an industrial solvent. DMSO was widely sold in hardware stores, health-food shops, and elsewhere, though often in impure, medically substandard formulations. Ironically, despite the fact that DMSO is a potent solvent with the unique ability to transmit poisons through the skin, it is legally sold only in bottles not labeled with instructions regarding human use because such instructions would have made the product subject to FDA regulation as a "misbranded" unapproved drug. The FDA's sanctions against Jacob have done nothing to settle the dispute over DMSO, and testing of the drug has resumed after 20 years of fruitless controversy.

The FDA has likewise delayed the development of the artificial heart for human subjects. Under the terms of the original investigational protocol for the Jarvik-7 artificial heart, the number of patients who may receive permanent implants is arbitrarily limited to seven; four of the operations have now been carried out. After prolonged and agonizing review, the FDA recently reaffirmed that no more than the three remaining permanent implants should be performed. The agency also authorized a limited number of temporary implants to be performed at four or five specially designated centers. Meanwhile, the FDA withdrew investigational approval of a new, smaller version of the Jarvik heart, designed for use in women and in patients with small chest cavities. The small Jarvik heart had been sent to a number of medical centers for emergency transplant cases, successfully saving the life of at least one woman, when the FDA ordered that all such devices be returned to the manufacturer. Jarvik himself has characterized the FDA's attitude by stating, "When it's an individual life-or-death situation, they don't disapprove. They don't want to say this person must die. But they want to avoid having the situation arise by keeping

everyone afraid to deal with it. They want the doctor to say 'no' to the patient." [36]

Because of its monopoly powers over drug testing, the FDA has been able to influence the direction of pharmaceutical research. In general, it has been agency policy to discourage the investigation of drugs that are not devoted to treating disease, such as drugs to extend memory, promote longevity, prevent cancer and degenerative diseases, or improve cosmetic appearance. Research on psychoactive drugs, like LSD, marijuana, and MDMA ("ecstasy"), has been virtually forbidden, although there is strong evidence that these drugs may have unique medical or psychological benefits. [37]

The rationality of the FDA's IND-approval criteria has never been convincingly demonstrated. In a 1977 study of FDA decision making, medical experts reviewed 30 IND decisions in two-member teams. In fully half the cases at least one team member disagreed with the FDA's decision; in five cases both team members disagreed. [38] The FDA has been especially zealous in discouraging what it regards as quack cures, many of them relatively innocuous, such as the supposed longevity drug GH-3 and the widely publicized anti-cancer drug Laetrile.

Consider the case of Laetrile. In 1970, the FDA turned down an IND application for Laetrile on the grounds that the chemical identity of the drug was not well specified. While this ruling effectively terminated the study of Laetrile for the better part of a decade, there remained some ambiguous evidence of possible weak efficacy. Given that Laetrile was relatively non-toxic, [39] especially in comparison with other cancer treatments at the time, a rational medical case could have been made for its use, especially in conjunction with other treatment, and it might at least have been beneficial as a placebo. [40] Nevertheless, the FDA prohibited its use altogether on the unproven grounds that it would lure patients away from potentially valuable therapy. In fact, the effect seems to have been to drive many Laetrile patients away from orthodox doctors and into the hands of dubious black-market practitioners. Meanwhile, 32 states parted company with the FDA (which is their prerogative in cases of intrastate commerce) by passing pro-Laetrile legislation.

In 1978, studies by the National Cancer Institute finally began to dispel the lingering scientific uncertainty over Laetrile's efficacy. Although the FDA appears to have been confirmed in its scientific judgment of Laetrile, its regulatory tactics were not notably effective. The case can be made that it would have been better for Laetrile to be openly exposed to public and scientific scrutiny, rather than legally proscribed on the mere grounds of regulatory violations. At the same time, steps might have been taken to help patients sue the drug's promoters for dishonest and misleading claims about its effects. [41] Despite FDA opposition, both Laetrile and GH-3 remain available on the black market.

Developmental-Study Design

The 1962 amendments require that new-drug efficacy be demonstrated in "well-controlled clinical studies"; by defining "well-controlled clinical studies," the FDA effectively dictates the design of drug investigation, which in turn determines the expense and duration of new-drug development. In practice, the interpretation of the efficacy-testing requirement has been an ongoing issue at the FDA, varying from one review officer to another. However, in line with its policy of strict testing standards, the FDA has generally interpreted the law as requiring at least two studies demonstrating the clinical efficacy of each new drug. [42] The necessity of multiple domestic testing is obviously debatable, especially in the case of dramatic medical breakthroughs.

Testing is divided into three phases. Phase I is toxicity testing, intended to determine a drug's side-effects and maximum safe dosage. Efficacy is not usually a consideration at this stage, although evidence of efficacy sometimes emerges, as it did in the recent case of the AIDS drug AZT. Phase I studies are small and may involve no more than a dozen subjects. Phases II and III are devoted to determining efficacy. In theory, Phase II consists of laboratory investigations and Phase III of clinical study, but in practice the distinction is often blurred. Study size varies but seldom exceeds a few hundred subjects.

An important precondition for Phase I testing is that the drug's toxicity be known or tested in animals.

Basic animal toxicity testing typically requires a couple of months. Further animal testing for carcinogenicity and other long-term effects is often required for NDA approval. Such tests may take many months to complete, but the FDA may allow them to be conducted concurrently with other, human studies. While it is generally agreed that some form of animal testing should precede human studies, the extent to which premature human testing has been hazardous is unclear. Half a dozen incidents have been recorded in which people were given drugs that later turned out to be carcinogenic in animals, one of which involved more than 3,000 patients; however, the total number of actual casualties is unknown.[43]

The FDA has been criticized for overemphasizing animal-toxicity studies, the results of which are often of dubious relevance because of the fundamental differences in physiology, biochemistry, and genetics between humans and animals.[44] Among the various drugs that have been withheld by the FDA on the basis of questionable animal data are the birth-control drug Depo-Provera and DMSO. Experts have questioned whether even aspirin or penicillin could be approved by the agency today, since both have dire effects on common laboratory animals. The FDA recently invoked the need for additional animal testing as an excuse to limit the use of artificial hearts, although developer Jarvik noted, "We've learned more in recent weeks [with humans] than in 20 years with animals." [45]

The FDA is noted for its strict insistence on fully controlled human studies for proof of efficacy. The agency's most important and controversial requirement in this regard is that efficacy be demonstrated through double-blind, placebo-control studies. As previously noted, the need for double-blind studies has been widely debated, and some experts have called for greater use of historically controlled, non-double-blind studies. However, it is generally conceded that double-blind studies are the surest and most effective way to resolve scientific uncertainty over drug efficacy, especially in cases where it might be marginal or palliative. Yet it is also agreed that double-blind studies pose ethical dilemmas, especially in the treatment of such degenerative or fatal diseases as ARC and AIDS. Many physicians have expressed qualms about withholding access to potentially beneficial medication from patients who would strongly prefer to have it.

Nevertheless, it has been aptly asked whether patients would enroll in double-blind studies if they could get a desired unapproved drug with certainty elsewhere. This question constitutes perhaps the single most compelling argument for restrictions on access to IND drugs. In practice, the problem can be mitigated through "crossover" studies, designed so that placebo patients are switched to the drug if and when it begins to show significant benefits for other patients. In the case of strongly effective drugs, crossovers may begin within a month or two of the start of testing. Although FDA-approved Phase II studies of AIDS drugs are, in general, designed to permit crossovers, AIDS investigators report that most test subjects express a strong preference for obtaining test drugs without the uncertainty attached to double-blind protocols.

One possible alternative to double-blind studies would be to test drugs by using sophisticated historical-control techniques in larger test populations. Economic costs could be held down by the elimination of placebo controls. In addition, since test subjects would be assured drug treatment, they might reasonably be charged for some portion of their treatment costs. The prevailing practice is for developers to pay the full costs of treatment themselves; however, AIDS patients participating in the voluntary Project Inform studies of isoprinosine and ribavarin are presently paying their own treatment costs. The ultimate problem with historical testing may be less economic than scientific: unfortunately, there are many circumstances in which historical controls seem unlikely to provide a suitable substitute for double-blind studies.

The remaining alternative would be to enhance the incentives for volunteers to participate in double-blind studies. Study participants could be offered increased compensation in the form of treatment, insurance benefits, or cash payments; or the cost of investigational drugs to non-participants could be increased by charging for "compassionate use." Given a sufficient differential in compensation, it seems reasonable that volunteers could be attracted to crossover double-blind studies.

Compassionate-Use INDs

The FDA grants compassionate-use INDs to patients suffering from dire and otherwise untreatable conditions. This criterion excludes many patients who might rationally wish to try experimental drugs. Thus, the FDA refused to grant compassionate use of isoprinosine to ARC patients, despite the fact that they face a substantial risk of developing AIDS. Likewise, FDA policy typically excludes compassionate-use INDs to patients suffering from such mundane though painful and irreversibly debilitating conditions as arthritis.

Even for patients with dire conditions, the FDA's interpretation of "compassionate use" is hardly liberal, as illustrated by the case of the dying Tucson heart patient described earlier. Following the uproar over the Tucson incident, the FDA announced that it would "not object if a physician chooses to use an unapproved device [though not drug] in such an emergency, provided that the physician later justifies to FDA that an emergency actually existed," with the understanding that it would be permitted only on a one-time basis.[46] Most foreign regulatory agencies appear to be more liberal in their compassionate-use policies than the FDA. French researchers have been reported to regard the FDA's policy on AIDS drugs as "barbaric." [47]

The FDA commonly rules out compassionate use whenever it feels that there is not enough evidence of safety or efficacy. FDA proscription typically applies to products that have not yet shown signs of efficacy in Phase II testing--one of the reasons the FDA has given for refusing compassionate use of AIDS drugs. However, given the inherent subjectivity of risk preferences there is little scientific basis for this prohibition. Even if the probability of harm from a new drug is greater than the probability of benefits, some patients may still rationally prefer a slim chance of hope to no treatment at all. In disregarding personal values and attitudes toward risk, FDA policy violates the essential meaning of "compassion."

Even when the FDA does permit compassionate drug use, patients often encounter resistance from physicians and drug manufacturers. Physicians must go to special effort to apply for a compassionate-use drug and must also, among other things, maintain special records and report test results. The paperwork for compassionate-use INDs can be burdensome, especially for independent practitioners with small staffs.[48] Few physicians, moreover, are aware of the existence of potentially valuable IND drugs in the first place, since they cannot be mentioned in advertising or promotion. FDA officials admit that the scarcity of information on compassionate-use drugs is a problem.[49] As for drug manufacturers, many are reluctant to supply compassionate-use drugs since they are required both to provide them and maintain detailed regulatory records free of charge. As noted earlier, these costs were the reason Newport Pharmaceuticals gave for declining to make isoprinosine available on a compassionate-use basis.

One final obstacle to compassionate drug use may come from product-liability and malpractice law. Recent trends in tort law have made it more difficult for consumers to assume legal responsibility for informed choice in risk. Drug manufacturers and physicians have accordingly been increasingly forced to refuse treatment out of fear of liability. The effect can be to deny freedom of choice to some patients.[50] Fundamental tort-law reform may therefore be needed to facilitate the informed assumption of risk by patients.

The Importation of Foreign Drugs

It is illegal to import unapproved drugs into the United States. Customs agents have confiscated foreign drugs even from patients with otherwise untreatable conditions who were importing them for personal use.[51] In theory, foreign drugs can be obtained by requesting IND approval from the FDA; however, the agency requires an explicit application from the patient's physician, and it generally does not permit consumers to pay for drugs so imported.

The FDA does sometimes permit travelers to bring limited quantities of certain unapproved drugs into the country as long as they are for personal use only. The agency typically considers imported drugs on a case-by-case basis, but a dozen or so commonly imported drugs are subject to "import alerts" signaling a more general prohibition. It is on this basis that imports of isoprinosine are presently permitted. The

quantity is strictly limited so as to prevent resale: AIDS victims are allowed only enough isoprinosine for a month. Technically, the agency's policy of permitting limited personal-use import of drugs contradicts federal regulations. Although the Reagan administration proposed in 1982 that the regulations be formally amended to permit personal-use import of unapproved drugs, the proposal was dropped at the insistence of FDA officials, who objected that it would permit consumers to bring harmful drugs into the country.

The foreign drugs singled out for interdiction in the FDA's "import alerts" include such largely innocuous but spurious pseudo-cures as Laetrile, GH-3, and various oriental drugs. Among the latter is the herb ginseng, which is freely available in health-food stores but is illegal when sold in packages labeled with therapeutic claims. The seizure of such drugs, after consumers have already paid for them, appears to be a heavy-handed form of consumer protection. The question has aptly been raised whether foreign-approved drugs might not be made more freely available. Some foreign countries automatically recognize approved drugs from other countries on a reciprocal basis.

Informed Choice and the FDA Approval System

There are two basic problems with the present FDA approval system. First, individuals are denied access to experimental therapies that may be of unique personal benefit. Second, regulation generally imposes economic costs and delays on new-drug research and development.

The first problem could be solved by legislation guaranteeing the right of patient access to unapproved drugs. FDA approval of the use of investigational drugs could simply be abolished, on condition that patients and their physicians be appropriately informed of the risks. At the same time, the importation of foreign drugs for personal use could be legalized. "Informed consent" could be broadly construed to require suitable testing and monitoring of patients, including special warnings in cases where toxicity was highly uncertain. Patients who did not want to know about medical risks could have the option of waiving warnings if they do desired.

Freedom of access to investigational drugs would not affect the standards or requirements for new-drug approval or the design of investigational studies submitted to the FDA in support of NDAs. Neither would it jeopardize the ability of companies to enlist experimental subjects for double-blind studies, since at worst they could withdraw drugs from availability until testing rolls had been filled. What it would do is abolish the requirement for FDA approval of compassionate-use INDs so that patients and physicians could arrange access to experimental products without FDA interference.

A major concern in eliminating FDA investigational-drug approval is that patients still be protected from needless exposure to hazardous practices due to negligence or quackery. This concern could be met by strict enforcement of informed-consent provisions. There is good reason to think that enforcement could be maintained without the FDA through liability and malpractice law, institutional review boards, and professional oversight, since these are the means whereby other kinds of risky medical practices (such as heart transplants and plastic surgery) are currently regulated.

The elimination of FDA surveillance could, however, increase the legal and ethical responsibilities surrounding informed consent and thus increase the risk of negligence. Informed consent could therefore be mediated by medical specialists in investigational drugs. Informed-consent agents could inform patients of the prospective risks and benefits of investigational drug therapy and ensure that physicians exercise appropriate precautions in treatment. Informed-consent agents could also insure patients against adverse reactions and/or malpractice and refuse to insure negligent treatments, such as the use of drugs that had not been tested in animals. In effect, informed-consent agents would afford decentralized, local assurance of investigational-quality standards in place of the centralized, inflexible standards now imposed by the FDA. Finally, information on investigational-drug use might be conveniently organized in a computerized data base, so that informed-consent agents and/or physicians could obtain and report up-to-date information on the safety and efficacy of investigational drugs. The FDA's present drug-reaction reporting system has been widely criticized as inadequate.

The second problem--excess costs and delays--could be mitigated by eliminating current constraints on drug research, so that researchers could pursue such studies as they thought reasonable above and beyond the "well controlled" scientific studies needed to get FDA approval for drug safety and efficacy. The cause of sound, orderly research would in no way be impaired or disrupted but rather would be speeded up and enriched by additional studies.

The Legal Sale of Unapproved Drugs

More fundamental reforms are needed to correct the broader economic distortions of drug lag caused by investigational-drug overregulation. In general, these distortions could be rectified by legalizing the sale of investigational drugs, thus recognizing the fact that FDA-unproven drugs can be of legitimate value to patients. By allowing drugs to be sold while testing was still in progress, promising but unproven drugs could be available sooner to people who might benefit from them. Economic obstacles to orphan-drug development would be reduced because companies could recoup costs during drug development: they could charge for compassionate-use treatment, using the revenues not only to fund research but to compensate experimental volunteers. The sale of investigational drugs would involve establishing a spectrum of safety and efficacy categories in the drug market, in place of the single category of FDA-approved "safe and effective." The classification "safe and effective" could still be used to designate drugs that had been thoroughly proven; however, other drugs would also be sold with appropriate informational warnings.

A common objection to the legal sale of unapproved drugs is that it would reduce the incentives of manufacturers to complete testing, thereby discouraging the development of "safe and effective" drugs. This abuse could be avoided by requiring that manufacturers continue to conduct efficacy testing of any unproven products they sell. However, because the demand for unproven drugs would probably be limited in most situations, given that manufacturers would be required to refrain from unsubstantiated claims about these products, it is likely that market forces would provide sufficient incentives to seek "safe and effective" approval. The major exception would be drugs for which it was uneconomical for manufacturers to conduct exhaustive testing, some orphan drugs, for example. It is precisely here that the strict testing required for FDA approval is irrational.

It is often objected that the legalization of unproven drugs could lead to a proliferation of pseudo-cures, like Laetrile. This problem could be largely averted by requiring that unproven claims be clearly designated as such and by creating a rating system to advise consumers and physicians of product efficacy. However, many medically dubious practices are in fact legal under the present system, including chelation, baboonheart transplants, and homeopathic drugs (which are officially sanctioned by a grandfather clause in the FDCA). There is no evidence that such therapies have been a major public health hazard, though harm may occur in individual instances. Nevertheless, a case can be made for stronger legal sanctions to compensate victims for damages from drug fraud. Because the FDCA has no provisions for restitution to fraud victims,[52] and class-action lawsuits for fraud are rarely practicable under current law, drug fraud can be a highly profitable venture. The maximum penalty assessed by the FDCA is \$1,000 and one year in jail for first offenses, or \$10,000 and three years in jail in the rare event that fraudulent intent can be proven. The potential rewards of drug fraud would be considerably reduced if the law were amended to award drug-fraud profits as compensation to victims.

Further research is needed to determine the best design for consumer drug warnings. A variety of warning devices could be used to distinguish products that were not proven "safe and effective." Patient inserts could perhaps suffice to designate such drugs as isoprinosine, which are relatively safe but of dubious efficacy. For riskier drugs, signed warning statements and/or formal informed-consent statements could be used. Special precautions would be necessary to assure appropriate monitoring and testing of patients using experimental drugs whose effects were highly uncertain. Each category of drug could be handled differently.

Experimental Substances. Drugs whose safety was basically uncertain would normally be used only in

Phase I or early Phase II laboratory studies, and their sale to consumers for treatment would typically be considered negligent. Such drugs would not be available for sale in pharmacies but might conceivably be sold to experimental researchers and treatment centers.

Developmental Products. Drugs whose toxicity was fairly well established and that had shown some signs of efficacy in human subjects could be made available at the opinion of the manufacturer for compassionate-use treatment. Developmental products would be sold with appropriate written and/or oral instructions to both patients and physicians and could not be promoted on the basis of unproven claims. Consumers would be advised of the product's unproven status and warned to beware unknown effects. Informed consent could be confirmed by a patient's signature at the physician's office, clinic, pharmacy, or informed-consent agency.

Trial Marketing. Drugs whose safety was well established and that had been proven effective in at least one well-controlled clinical study could be introduced to the market on a "trial marketing" basis. Trial-marketing drugs could be sold with prominent written and/or oral warnings to beware possible unknown effects. Physicians and patients would be directed to report adverse reactions for post-marketing surveillance. Trial marketing would afford better warnings than are currently provided for newly approved drugs, which are sold without any way to distinguish them from older, proven products. Because it is rarely practical to test drugs in more than a few hundred subjects, it is generally impossible to detect rare reactions, which often affect fewer than one in a thousand patients, through testing. Drugs could accordingly remain in the trial-marketing category until they had proven themselves for at least a year in a sizable patient population.

Proven Safe and Effective. Drugs whose safety and efficacy were thoroughly demonstrated after a period of trial marketing could be designated as generally "safe and effective." These drugs would normally be safer than newly approved FDA drugs under the present system, most of which are placed on the market after only limited testing.

Special Alerts. Drugs that were found to be unusually hazardous or whose efficacy was in question would be identified by special warnings. Drugs already rated "safe and effective" would be subject to prompt reclassification if evidence arose of lack of safety or efficacy or if they became obsolescent. The present law makes it difficult for the FDA to remove an obsolete, dangerous, or ineffective drug from the market once it has been approved.[53]

Foreign Drugs. The ban on the importation of foreign drugs would be lifted. Foreign drugs could then be sold in a manner similar to how trial-marketing or developmental drugs are sold, except in cases where evidence indicated they were unusually harmful.

The foregoing measures would afford greater protection from dangerous drugs than under the present system. There would be less pressure on the FDA to approve drugs as "safe and effective," since newer drugs could be sold as trial-marketing or developmental products. Improved drug warnings would raise consumer safety consciousness. Product alerts could be applied to many "old" prescription drugs that are commonly misused or misprescribed--an important option because the misuse of old drugs may in fact be a greater public health problem than exposure to hazardous new drugs.[54]

Investigational-drug treatment could be provided economically by specialized research centers with expertise in the use and development of experimental drugs. One such center is Biotherapeutics, a private company in Franklin, Tennessee, that provides patients with state-of-the-art cancer treatment based on monoclonal antibody techniques that do not require IND approval.

Manufacturers who chose to sell investigational drugs would naturally be exposed to the risk of product-liability suits. Given the substantial cost of consumer liability awards and the recent trend toward strict liability in product-liability law, many manufacturers might be unwilling to enter the investigational-drug market. Recent court decisions have even held some manufacturers liable for drug reactions that were clearly unavoidable and publicly known as such. This has threatened to push some FDA-approved

products from the market: recent examples include whooping-cough vaccine and the morning-sickness drug Bendectin.

The case can be made that the present liability system strongly overcompensates accident victims[55] and that awards should be restricted to cases of avoidable harm.[56] In effect, liability law undermines freedom of choice in drug use by forcing consumers to overinsure against potential accidents. It seems impossible that investigational drugs could be sold economically under conditions of strict liability. Neither would it seem appropriate to hold manufacturers to the more traditional drug-liability doctrine, under which they are liable for any adverse reactions they have not warned about specifically.

Since experimental-drug use would inevitably entail a significant risk of previously unknown reactions, it seems reasonable that patients should assume some of the risk themselves, provided that the manufacturer is not negligent and gives adequate warning of the risk of unknown reactions. Unfortunately, the inherent uncertainty of investigational-drug risks makes it difficult to give a precise definition of "negligence" or "adequate warning." Developers might therefore still be faced with an unacceptable insurance burden in selling unapproved drugs. This problem could be mitigated if developers offered customers a specific, reasonable, but limited level of no-fault insurance coverage for unknown reactions. The level of coverage could be scaled according to the developmental status of the drug, beginning with a low level for highly experimental products and increasing to full liability for drugs proven to be "safe and effective."

Conclusion

The best solution to drug overregulation would be a policy of informed choice in drug safety and efficacy. An informed-choice program would involve reducing the FDA's powers to restrict drug sales and use, while establishing the necessary informational structures to ensure informed consent. Specific reforms would include:

- * the elimination of mandatory IND approval;
- * legalizing the sale of unproven drugs under a system of graded safety and efficacy ratings;
- * strict enforcement of informed-consent, productsafety, and product-efficacy warnings, with restitution to victims in the case of fraud;
- * an improved consumer-drug warning system, featuring patient package inserts and signed warning statements;
- * the use of independent informed-consent agents to mediate informed consent and insure against adverse reactions;
- * the limitation of product liability to cases of avoidable negligence, with no-fault insurance coverage for unknown reactions;
- * legalizing the importation of foreign drugs.

These measures could be implemented within the framework of the present approval system by amending the FDCA accordingly. However, none of them need be enforced by federal regulatory agencies. Many functions of FDA regulation might be performed as well or better through private means: private consumer groups and medical boards could provide timely and meaningful drug information, drug fraud could be controlled through class-action lawsuits organized by consumer groups, and the responsibility of safety certification could be assumed by industry insurance or drug-compensation boards.[57] In principle, consumer-health insurers might have the best incentives and resources to oversee drug safety and efficacy, and an independent consortium of health insurers might therefore be an attractive long-range alternative to the FDA.[58]

In the end, informed choice requires a rethinking of the present paradigm of medical decision making. The essential insight is that drug safety can be meaningfully defined only in terms of individual choice, not society-wide judgments of "safety and efficacy." Regulatory approval is by nature a clumsy mechanism that does nothing to resolve ethical dilemmas or scientific disputes. By providing consumer choice in drug safety and efficacy, the economic and ethical dilemmas of the present regulatory system could be eliminated. Drug safety would be promoted by helping individuals make informed decisions, not limiting their choices, and patients who could potentially benefit from that freedom--whether AIDS or arthritis victims--would not be sacrificed in pursuit of an arbitrary, bureaucratically imposed notion of the public interest. AIDS victims should not be victimized by the U.S. government.

FOOTNOTES

[1] Richard F. Harris, "AIDS drug dilemma," San Francisco Examiner, December 1, 1985, p. A24.

[2] Quoted in Daniel Henninger, "Surgeons vs. The Bureaucracy," Wall Street Journal, February 27, 1986, p. 24.

[3] Wall Street Journal, March 14, 1986, p. 6.

[4] Conversation with an investigating physician.

[5] Telephone conversation with FDA review officer, commenting on Philip J. Hilts's Washington Post story "Possible AIDS Drugs to Be Tested on Thousands," March 13, 1986, p. 1.

[6] Randy Shilts, "The Smuggling of Illegal AIDS Drugs," San Francisco Chronicle, October 21, 1985, p. 12.

[7] George Stanley, quoted in Harris.

[8] Quoted in Harris.

[9] Tamara Jones, "AIDS patients from U.S. look for hope in Tijuana drugstore," San Francisco Examiner, December 22, 1985, p. A3.

[10] Ann Giudici Fettner, "Making Life Illegal," New York Native, September 30/October 6, 1985, pp. 21-23.

[11] Sources in the research community report that they expect a study of combined use to be approved shortly but that ARC patients will likely be excluded.

[12] "Drug Research--Life-or-Death Issue for S.F.'s AIDS Victims," San Francisco Chronicle, October 21, 1985, p. 12.

[13] Shilts.

[14] George Stanley, quoted in Harris.

[15] Subjectivity of risk is a fundamental axiom in the theory of decision analysis, which is generally accepted as the basis of the economic theory of risk. Decision analysis is also being increasingly applied in medical decision making. For an exposition, see Ronald Howard and James Matheson, eds., *The Principles and Applications of Decision Analysis* (Strategic Decisions Group, Menlo Park, Calif., 1983). For a medical perspective on subjectivity of risk, see Stephen Eraker and Harold Sox, Jr., "Assessment of Patients' Preferences for Therapeutic Options," *Medical Decision Making* 1, no. 1 (1981): 29-39.

[16] Friedrich Hayek, "The Use of Knowledge in Society," in *Individualism and Economic Order* (Chicago: University of Chicago Press, 1948), p. 80.

[17] Murray Weiner, "Should the Public Have the Right to Use Unproven Remedies? Yes.," in *Controversies in Therapeutics*, ed. Louis Lasagna (Philadelphia: W. B. Saunders, 1980), pp. 491-93; Durk Pearson and Sandy Shaw, *Life Extension* (New York: Warner Books, 1980), pp. 590 ff; Dale Gieringer, "Consumer Choice and FDA Drug Regulation" (Ph.D. diss., Stanford University, 1984); idem, "The FDA's Bad Medicine," *Policy Review* 33 (Summer 1985): 71-73; and idem, "The Safety and Efficacy of New Drug Approval," *Cato Journal* 5, no. 1 (Spring/Summer 1985): 177-201.

[18] Peter Temin, "The Origin of Compulsory Drug Prescriptions," *Journal of Law and Economics* 22 (April 1979): 91-105.

[19] *New York Times*, February 26, 1983, p. I48.

[20] Milton Silverman and Philip R. Lee, *Pills, Profits, and Politics* (Berkeley: University of California Press, 1974), pp. 282-304; and Peter Temin, *Taking Your Medicine* (Cambridge: Harvard University Press, 1980), pp. 88-119.

[21] D. E. Kanouse, S. H. Berry, B. Hayes-Roth, W. H. Rogers, and J. D. Winkler, "Informing Patients About Drugs: Summary Report on Alternative Designs for Prescription Drug Leaflets" (Santa Monica, Calif.: Rand Corporation, August 1981), p. 3.

[22] Morton Mintz, *The Therapeutic Nightmare* (Boston: Houghton Mifflin Co., 1965), p. 261.

[23] Robert L. Brent, "Drug Testing in Animals and Teratogenic Effects: Thalidomide in the Pregnant Rat," *Journal of Pediatrics* 64, no. 5 (1964): 762-70.

[24] Henry Grabowski and John Vernon, *The Regulation of Pharmaceuticals: Balancing the Benefits and Risks* (Washington: American Enterprise Institute, 1983), pp. 29-30.

[25] William Wardell and Louis Lasagna, *Regulation and New Drug Development* (Washington: American Enterprise Institute, 1974).

[26] General Accounting Office, *Report to the Subcommittee on Science, Research and Technology of the House Committee on Science and Technology*, May 28, 1980.

[27] Sam Peltzman, *Regulation of Pharmaceutical Innovation: The 1962 Amendments* (Washington: American Enterprise Institute, 1974).

[28] *Hearings of the Subcommittee on Science, Research and Technology of the House Committee on Science and Technology on the FDA's Process for Approving New Drugs*, 96th Cong., 1st sess., 1979.

[29] "Proposed New Drug, Antibiotics and Biological Drug Product Regulations," *Federal Register*, October 19, 1982; June 9, 1983; February 22, 1985.

[30] For a compendium, see Kenneth Anderson, *Orphan Drugs: Your Complete Guide to Effective, Tested Medications Outside the U.S.--and Their Availability* (New York: Linden Press, 1983).

[31] Gieringer, "Safety and Efficacy."

[32] Henninger.

[33] Rita Ricardo-Campbell, "Drug Lag: Federal Government Decision Making," *Hoover Institution Studies* no. 55 (Stanford, 1976), pp. 49-50.

[34] *Science News*, February 12, 1983, p. 100, emphasis in original.

- [35] Pat McGrady, Sr., *The Persecuted Drug* (New York: Grosset and Dunlap, 1973).
- [36] Quoted in Henninger.
- [37] The regulation of psychoactive drugs is shared by the FDA and the Drug Enforcement Administration under the Controlled Substances Act.
- [38] Department of Health, Education and Welfare, *Interim Report: FDA's Review of Initial IND Submissions, a Study of the Process for Resolving Internal Differences and an Evaluation of Scientific Judgments*, May 31, 1977.
- [39] A couple of accidental poisonings from Laetrile overdoses were reported. See Victor Herbert, "Laetrile: The Cult of Cyanide Promoting Poison for Profit," *American Journal of Clinical Nutrition* 32 (May 1979): 1121-58.
- [40] On the medical case for the use of Laetrile, see Weiner, pp. 483-93.
- [41] For evidence of deliberate deception in Laetrile's promotion. see Herbert.
- [42] In certain cases, the FDA allows multi-center studies to count as fulfilling the multiple-testing requirement; also, orphan drugs can qualify for special treatment.
- [43] J. O. Nestor, "Results of the Failure to Perform Adequate Preclinical Studies Before Administering New Drugs to Humans," in *Hearings*, pp. 1289-98.
- [44] Wardell and Lasagna, pp. 19-21, 137-39, 145-46.
- [45] Quoted in Henninger.
- [46] Conversation with an official in the Medical Devices division of the FDA, citing an FDA regulation.
- [47] Shilts.
- [48] The Reagan administration has reformed FDA regulations to allow drug companies to file "blanket" compassionate INDs so that individual physicians need not apply separately to the FDA; however, it does not seem to have had a major impact on the workload of physicians.
- [49] Conversation with an FDA review officer.
- [50] Product liability is said to have been a consideration in Newport Pharmaceuticals's decision not to distribute isoprinosine for compassionate use, according to a company spokesman.
- [51] Prior to September 1985, isoprinosine and ribavarin were confiscated from AIDS patients by some customs officials. In a famous incident, the anti-epileptic drug valproate was seized from a family with a child suffering a severe form of epilepsy not otherwise treatable. See the testimony of J. Kiffin Penry in *Hearings*, p. 101.
- [52] William Goodrich, "Restitution--Modern Application of an Ancient Remedy," *Food-Drug-Cosmetic Law Journal* 9 (October 1954): 565-72.
- [53] Paul Quirk, "Food and Drug Administration," in *The Politics of Regulation*, ed. James W. Wilson (New York: Basic Books, 1980), pp. 191-235.
- [54] Wardell and Lasagna, pp. 100-103.
- [55] See Patricia M. Danzon, "Tort Reform and the Role of Government in Private Insurance Markets,"

paper presented at Conference on Policy Options for Catastrophic Injuries, Hoover Institution, Stanford, October 21-22, 1983.

[56] See Richard A. Posner, *Economic Analysis of Law*, 2d ed. (Boston: Little, Brown & Co., 1977), pp. 134-42; and Roland McKean, "Product Liability: Trends and Implications," *University of Chicago Law Review* 38 (1970): 3-63.

[57] See David Leo Weimer, "Safe--and Available--Drugs," in *Instead of Regulation*, ed. Robert Poole (Lexington, Mass.: D. C. Heath, 1982), pp. 239-84.

[58] National health insurance plays a primary role in drug certification in some foreign countries, notably New Zealand. See William Wardell and A. W. S. Thompson, "New Zealand," in *Controlling the Use of Therapeutic Drugs*, ed. William Wardell (Washington: American Enterprise Institute, 1978), pp. 217-18.