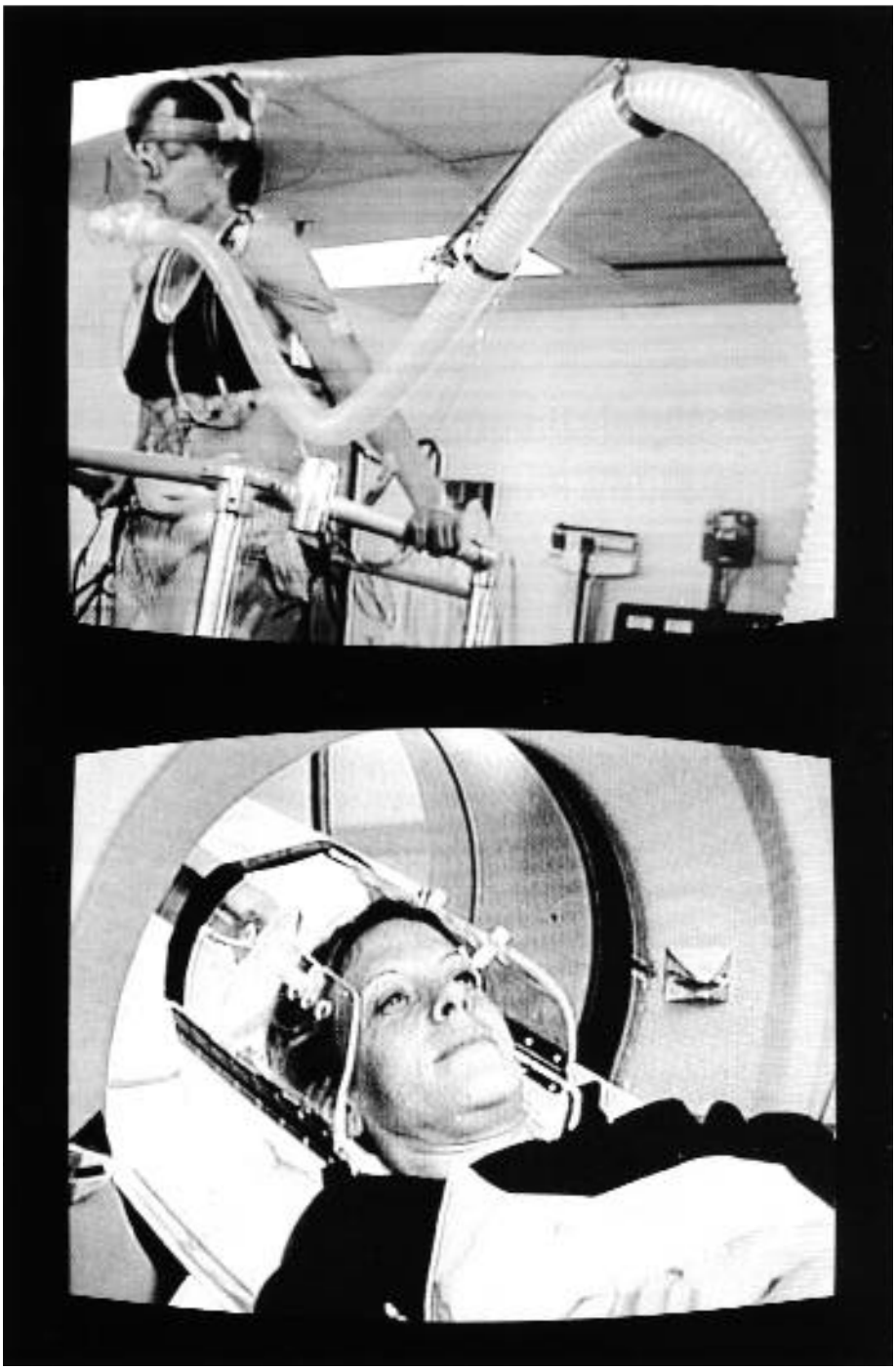
Protecting Human STUDY SUBJECTS

In 1963, a New York hospital allowed some elderly, ill, and feeble patients to be injected under the skin with cancer cells to study immune response. Patients were not told what the injections were—just that their "resistance" was being measured. Nothing came from this ill-conceived effort, which was intercepted and stopped soon after it began, with none of the patients getting cancer.

In early 1994, the federal government released documents detailing hundreds of radiation experiments performed on thousands of civilians and military personnel decades ago, apparently in some cases without adequate knowledge or consent. Experiments included giving food mixed with tracer doses of radioac-



Known as Institutional Review Boards, or IRBs, these committees of experts and lay persons also review the research as it goes along.

tive substances to subjects and injecting infants with radioactive iodine.

These are worst-case examples of failure to inform and protect human subjects used without their knowledge in drug testing and medical experimentation. They are not remote historical events. The cancer injections were stopped over 36 years ago. The radiation experiments occurred in the 1940s and 1950s.

Such disregard for the rights and welfare of study subjects is far less likely today. Review boards at hospitals and research institutions throughout the country make sure participants are fully informed and willing before studies ever get under way. Known as Institutional Review Boards, or IRBs, these committees of experts and lay persons also review the research as it goes along. Watching these watchers are FDA and other federal agencies such as the National Institutes of Health (NIH), whose rules are designed to protect those taking part in medical research.

In 1976, FDA issued regulations requiring IRB review of all studies using institutionalized subjects. Regulations amended in 1981 require all studies needing a FDA research permit to be reviewed and approved by an IRB before tests on humans can begin, whether or not subjects are in an institution.

Edmund Pellegrino, M.D., professor of medicine at Georgetown University in Washington, D.C., and an internationally recognized expert on medical ethics, says that using human subjects to advance scientific knowledge is acceptable "as long as there is informed consent and the rights of the subjects are respected."

In an instructional videotape prepared by FDA, Pellegrino says persons entering a study must be told they are "willing volunteers" who can stop or even leave the study at any time if they become stressed or apprehensive, or suffer too great discomfort, or simply wish to go no further.

The first responsibility of the physician is to "do no harm," and there are few that set out to violate that principle. But at the extreme of those who did were scientists convicted at the 1946 Nuremberg trials of conducting experiments on concentration camp inmates. From these trials came the Nuremberg Code, the first modern-day formal statement on medical ethics, and a precursor to the Belmont Report, the basic foundation upon which the present U.S. standards for the protection of human subjects of research rest.

Informed consent was added to the requirements of the Federal Food, Drug, and Cosmetic Act by the 1962 Kefauver-Harris Amendments. A signed consent document was not required, only a notation in the chart that verbal consent had been obtained. A 1967 FDA policy statement outlined the consent process and required consent to be obtained in writing for early stages of research.

The U.S. Public Health Service (PHS) in 1966 defined the right of subjects to be told about the benefits, risks, and purpose of the research for which they are volunteering. It made this "informed consent" a condition of PHS funding for research grants, which includes all NIH-funded studies, but not FDA-regulated studies, unless they are also federally funded.

A decade later, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research developed three basic principles governing research involving human subjects that were published in the Belmont Report. The principles are: (1) respect for persons, the requirement to treat individuals as autonomous agents, and the requirement to protect those with diminished autonomy; (2) beneficence, maximizing possible benefits and minimizing possible harms, and; (3) justice, as demonstrated by fairness in distribution of the opportunity to participate in research. The Belmont Report is the basis of the present human subject protection regulations in the United States, which have been now adopted largely unchanged as international standards in the International Conference for Harmonization. The U.S. informed consent regulations contain two exceptions to obtaining the informed consent of an individual

before entering him/her into a study: (1) an unplanned situation, when use of an investigational material is required to save the life of the individual, and (2) a planned study that must be done in the emergency room in order to evaluate use of the test article in that setting. This exception is limited to situations where the intervention must be started in order to save the life of the subject and there is not time to obtain consent. This second exception requires FDA approval before the study is started, IRB approval, and public disclosure to the community of a summary of the research and that the research is being done without obtaining informed consent. The material provided to the public is available from FDA through the provisions of the Freedom of Information Act.

Before it will approve a new drug or device for marketing, FDA requires evidence of the product's safety and effectiveness from the manufacturer. The first evidence of safety is obtained from laboratory tests and tests in animals. If favorable test results are obtained, testing in humans may begin. The entire testing process can take a number of years, with only a small percentage of the drugs, biologics, and devices meeting all of the safety and effectiveness requirements to be approved for marketing.

Persons taking part in clinical trials are not necessarily patients in hospitals and institutions. Many are patients of private practitioners involved in clinical research. Many are not patients at all, but are healthy individuals who have been recruited for a study through a newspaper ad, poster, or other source. FDA's IRB and informed consent regulations ensure that research subjects are informed and willing participants and that their health and safety are not unnecessarily endangered.

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An IRB comprises at least five people with varying backgrounds including physicians, scientists, non-scientists, and at least one person not affiliated with the research institution. Maintaining a membership with diverse training helps an IRB stay objective. An IRB should use consultants as needed to assist in the review of studies requiring specialized knowledge not held by the IRB members. The IRB must also be able to determine the acceptability of the research in terms of applicable law, standards, or professional conduct and practice.

The IRB meets to review the protocol, or research plan, for the proposed project and may approve or disapprove it or make changes before granting approval. It also must review and approve, modify, or disapprove the informed consent form to be presented to prospective research subjects. The IRB also conducts continuing review at least annually while research is under way. IRB review ensures that:

- Risks to subjects are minimized. Procedures must be used that are consistent with good research design and do not expose subjects to unnecessary risk. If the subject is a patient, the study must be designed and conducted in a way that does not adversely affect the patient's progress.
- Informed consent is obtained and documented from each subject or the subject's legal representative.
- Selection of subjects is fair and equitable, and there are safeguards to protect subjects, such as the mentally retarded, who may not be able to look out for their own interests.
- Risks to subjects are reasonable in relation to expected benefit to those subjects and the importance of the knowledge that may be gained.
- Provisions exist to protect the privacy of subjects and to maintain data confidentiality.

IRBs also ensure that appropriate additional safeguards are in place to protect the rights and welfare of vulnerable populations, such as women, children, prisoners, those with mental disabilities, and persons who are economically or educationally disadvantaged.

Periodically, FDA inspects IRB records and operations to certify that approvals, human subject safeguards (including informed consent), membership, and conduct of business are what they should be. Sometimes

these inspections yield evidence of problems, such as in 1993 when FDA imposed penalties on a large California university IRB for infractions that included failure to report deaths.

Informed consent, which is one of three elements in protecting the rights and welfare of study subjects, is not simply a matter of having the subject sign a piece of paper. It requires that the researcher:

- give the subject adequate information about the study;
- respond fully to the subject's questions and be certain that the subject understands all the risks and responsibilities that participation entails;
- ensure that the subject (if a patient is receiving treatment, for example) is aware of other options, along with their advantages and disadvantages; and
- obtain the subject's voluntary consent to take part.

Researcher and subject should discuss the study and the subject's role in it until both are satisfied that the subject can make an informed decision about whether to participate.

In July 1993, FDA released new guidelines for including women and minorities in clinical research. The guidelines promote recruitment of women and minority participants and foster understanding of cultural nuances. In March 1994, the National Institutes of Health published guidelines implementing a new statutory requirement that women and minorities be adequately represented in federally funded research. IRBs, together with investigators and institutional officials, will play important roles in ensuring compliance with these guidelines.

How an IRB fulfills its role can be seen in a Georgetown University study into the effects of strenuous exercise on blood clotting. The study involved healthy young female runners recruited through the campus newspaper. Runners had blood drawn before and after treadmill exercise, with the fibrin (blood-clotting) time recorded. Blood pressure, heart rate, and respiration also were recorded.

Participants knew that findings might help determine whether exercise is desirable for persons recovering from heart attacks. The study also benefited participants by allowing them to better understand their own physiology when running, an aid when deciding whether to stay in competition. Also, participants and their doctors were informed of any health problems that showed up during the study.

Before approving the study, the IRB at Georgetown University asked that participants be told that the study followed earlier successful research on male athletes; that the total blood drawn would be one-quarter that of a routine blood donation; and that, although it was a low-risk study, emergency equipment would be on standby. The IRB found it a big plus that the physician doing the research had gone through the blood and treadmill test herself when the study was designed.

Pellegrino stresses that study subjects must not be coerced or misled by researchers, who often do not realize how little the subjects understand. He says that patients receiving treatment who are asked to join a study "can easily confuse the experiment with their treatment." He also acknowledges that some scientists feel IRB review "somehow interferes with that research."

FDA does not require that subjects be compensated if there is injury or other unfavorable result. But in any study that involves more than minimal risk, the subjects must be told in the informed consent interview before they enter the study whether compensation and medical treatment are available and what the compensation consists of or how to obtain further information about it. The informed consent form must include an accurate summary of this information.

An additional layer of review sometimes used is an independent Data and Safety Monitoring Board (DSMB). At periodic intervals during the study, this board reviews accumulated data. The DSMB may recom-

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mend stopping the study if the data show either (1) the test article is clearly superior, and all subjects should receive it, or (2) the test article is clearly inferior, in which case, none of the subjects should continue to receive it.

Present FDA policy requires that only under certain circumstances may sponsors charge clinical investigators or research subjects for investigational drugs. A firm intending to charge for experimental drugs must first justify the charges to FDA. Companies sponsoring research with investigational medical devices, however, may generally charge the investigator for the cost of the device. The investigator in turn can pass that charge on to the subject, but no profit is to be made from the experimental drug or device. Subjects must be told before they enter a study whether they will be charged for services or products as a result of taking part in the study, and the IRB must be aware of and approve such proposed charges. The informed consent document must outline any additional costs that will be billed to study subjects or their insurance companies as a result of participation in the study.

The informed consent whether oral or written, shall not contain any wording through which the subject waives or appears to waive any legal rights or releases or appears to release anyone involved in the conduct of the research from liability for negligence. The subjects may not be asked to waive ownership rights in blood or tissue samples as a condition for entering a study, particularly, a study that involves treatment for their diseases. The subjects do not waive the right of privacy; however, the consent form should explain that FDA can inspect and copy medical records as part of its approval process for drugs, biological products, and devices. Usually, FDA does not copy the names of the individual subjects—only study results.

FDA regulations permit use of a test article (drug, biological product, or device) without prior IRB review when a life-threatening condition exists; when no standard acceptable treatment is available; and when there is not time for IRB approval. This means an investigator may, in a life-threatening emergency, use a device or administer one course of treatment to a subject without IRB review. This was done in the 1980s at the University of Arizona Medical Center, when an artificial heart, not yet approved by FDA, was used in a subject for three days as a "bridge" until a human replacement heart could be found.

If a project carries no greater risk than having a routine physical examination, FDA regulations permit an IRB to use an "expedited review." This means that the research can be reviewed and approved by the chairman or senior members without convening the full IRB. Minor changes in an existing project also can be approved through an expedited review.

Institutions engaged in research involving humans will generally have their own IRBs that review work done on the premises or elsewhere by the staff of the institution. However, the IRB need not be "onsite" at the institution as long as it is available to review that institution's research. An IRB in a hospital, for example, is not required to review studies done outside the hospital's jurisdiction, but the IRB may do so if the hospital is willing.

IRB members usually are not paid for their services, but there is nothing in the regulations to prevent it. Any payment should be a fixed amount and not contingent upon a favorable review. Travel and other expenses may be reimbursed.

The FDA relies upon the careful review by the responsible IRB to ensure that the research studies are not unnecessarily risky and are valid endeavors. The IRB also assures that the process for subject selection is fair and that the subjects are adequately informed about the anticipated risks and hoped-for benefits of participation. Together, these principles serve to protect the rights and welfare of research participants.

FDA Finds New Ways to *Speed Treatments* to Patients

Moviegoers in the ’30s and ’40s were regularly treated to the high drama of a dying patient whose only hope lay in an experimental drug—usually called a “serum”—that had to be flown through a raging storm, at night, to the patient’s bedside. In the Hollywood scenario, the “serum” always arrived in the nick of time; the patient was saved, the brave young doctor was acclaimed a hero with a brilliant future, and the world got a miraculous new weapon in the battle against death and disease.

MUSIC UP—FADE TO BLACK—ROLL CREDITS

Such movies are, of course, fantasy. But underlying their dated and, by today’s standards, corny plot lines is the widely held belief that when nothing else can help, desperately ill patients ought to have access to investigational treatments that show some evidence of being useful. Concerned health professionals and consumers alike have long maintained that even though possibly important new drugs or biologicals haven’t yet completed the complex and often lengthy path to FDA approval, physicians should nonetheless be able to use them in willing patients who can’t benefit from established therapy.

And, in fact, thousands of people receive investigational products, not only in carefully controlled clinical trials, but also in innovative programs aimed at giving them all the medical help possible.

Using investigational agents in a sort of last-ditch effort to help desperately ill and dying patients is not new to medicine. FDA has permitted the emergency use of unapproved, investigational products for many years. Under the general rubric “compassionate use,” the agency has permitted sponsors of investigational agents to provide them to doctors not involved in controlled clinical trials for use in individual patients who might be helped by the treatment.

In 1987, FDA changed its regulations on investigational new drugs (INDs) to specifically authorize treatment use of such agents. The term “Treatment IND” highlights the fact that an investigational agent is being administered not primarily to gain

information about its safety and effectiveness, as in a controlled study, but to treat certain seriously ill patients.

The change in terminology is emblematic of a shift in the way FDA, the Congress, the pharmaceutical industry, health professionals, and health activists view the role of drug development and drug regulation in this country. All agree that a major goal of drug regulation must be to speed the journey from laboratory to bedside of important new drugs for devastating illnesses.

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The shift involves more than just wider treatment use of unapproved agents. It also encompasses steps to accelerate FDA's process for reviewing applications to bring new drug and biological products to the market. Without compromising the approval requirements for safety and effectiveness of new drugs and biological products, FDA has taken numerous steps to shorten the time devoted to preapproval drug testing. This streamlining of the process is geared toward eliminating unnecessary, duplicative studies, and expediting the review of innovative agents for the most serious or life-threatening conditions.

Through published guidelines and meetings with sponsors, FDA reviewers help drug developers plan studies designed to generate the information FDA needs to make decisions about approvability. In addition, under a new congressional mandate, the agency will be able to collect user fees from product developers and manufacturers to cover the costs of expediting the review of prescription drug applications.

Treatment INDs

The first class of drugs to generate interest in treatment use outside formal clinical trials consisted of beta-blocking agents used in certain forms of heart disease. During the mid-1970s, many thousands of patients were treated with beta blockers for advanced, life-threatening heart and lung conditions for which no effective alternative treatment existed. In one instance, more than 600 cardiologists treated some 20,000 patients with the antiarrhythmic drug amiodarone before it was approved for marketing as Cordarone in late 1985.

By far the most celebrated use of a Treatment IND involved expanding the availability before approval of zidovudine, commonly known as AZT, to people with AIDS. Initial (phase 1) testing of the drug in 33 patients with AIDS, carried out between July and December of 1985, yielded encouraging results. Phase 2 trials to assess the drug's safety and effectiveness began in February 1986. About 300 people with AIDS at several centers around the country were randomly selected to receive either AZT or a placebo.

These studies were abruptly halted in September 1986 when it was discovered that 19 patients receiving placebo had died, while only one death had occurred among those receiving AZT. Within a week of receiving this information, FDA authorized a treatment protocol for AZT. As a result, more than 4,000 AIDS patients were treated with AZT before its approval as the first anti-AIDS drug under the brand name Retrovir in March 1987.

Building on that and other experience with treatment protocols, FDA developed and issued in May 1987 regulations codifying the circumstances under which Treatment INDs could be granted. While the purpose is to make promising investigational drugs available as early as possible to patients with serious or immediately life-threatening diseases, the Treatment IND regulations also ensure that, despite possibly extensive treatment use of an investigational agent, carefully controlled trials will go forward to demonstrate the drug's safety and effectiveness.

The regulations reiterate the requirement that, as with all clinical use of investigational drugs, informed patient consent must be obtained, and the product cannot be promoted or otherwise commercialized. FDA also requires that a product administered under a Treatment IND must be under (or have completed) active clinical investigation, and its sponsor must be pursuing marketing approval with "due diligence."

It's critically important to complete definitive clinical trials, because once an investigational product appears in early studies to offer an important therapeutic advance and becomes

available for treatment use, "you may never get another crack at it," says Robert Temple, M.D., director of FDA's Office of Drug Evaluation I. "If a study looks favorable—seems to show an effect on survival, for instance—physicians are very reluctant to redo the study. They want the active drug for their patients."

Ethical concerns make it difficult for physicians to withhold a promising investigational drug that might forestall severe disability or death. But if the study that showed promise was not well-designed—if, for example, there was no control group—what looked like favorable results may prove to be an illusion. "So it's very important to do a good study early—right at the beginning before impressions form that might turn out to be wrong," Temple says.

He points out that the early clinical trial showing AZT to be effective in AIDS patients was a placebo-controlled study, the results of which were dramatic and unequivocal. On the other hand, in the case of ganciclovir, an antiviral drug used to treat an eye infection in AIDS patients, the path to treatment use and ultimate approval was quite different. Early suggestions of ganciclovir's effectiveness led to wide use before controlled clinical trials ever started.

Ganciclovir was approved in 1989 on the basis of a historical comparison with other treatments. But, Temple maintains, approval of ganciclovir was almost certainly delayed for years by the lack of appropriate, controlled clinical investigation.

FDA has indicated, for purposes of Treatment INDs, what constitutes serious or immediately life-threatening illness, what scientific information about the drug's safety and potential usefulness must be in hand, and how physicians can obtain investigational drugs for treatment use.

As of August 1994, 29 agents had been granted Treatment IND status. The conditions for which they have been used include AIDS and its complications, control of infection in kidney transplant patients, severe obsessive-compulsive disorder, Alzheimer's disease, severe Parkinson's disease, various advanced cancers, and respiratory distress syndrome in premature infants. At press time, 24 of these drugs had been approved by FDA and are on the market.

Other Quick Help

An older, more targeted treatment-use initiative is aimed at making investigational cancer drugs available to patients who are not participating in controlled clinical trials. Since the mid-1970s, FDA has reviewed drugs for limited distribution by the National Cancer Institute (one of the National Institutes of Health) to provide promising new anticancer drugs and drug combinations to cancer patients for whom established therapy is ineffective.

Another mechanism to permit wider availability of experimental agents is the "parallel track" policy developed by the U.S. Public Health Service in response to the AIDS epidemic. Under this policy, patients with AIDS whose condition prevents them from participating in controlled clinical trials can receive investigational drugs shown in preliminary studies to be potentially useful. At press time, one drug (D4T) had been made available under the parallel track mechanism. D4T was approved for marketing in mid-1994.

Streamlining Review

Less dramatic, perhaps, than rushing investigational drugs to the desperately ill, but almost certainly of more long-range benefit to society, are measures to streamline FDA's review and approval process and expand the agency's resources for this task. Although not the stuff of which gripping movies are made, these efforts can mean earlier arrival of important new drugs in hospital and community pharmacies for the benefit of everyone who needs them.

One change FDA has adopted in recent years to speed drug review is categorizing new drugs as either standard or priority. Standard drugs are those that offer only minor improvement (or none) over drugs already on the market. Priority drugs, on the other hand—which may in fact be a new dosage form of, or new use for, an existing drug—are believed to represent potential major advances in healthcare.

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Distinguishing the two categories of drugs permits speedier review even before a new drug application is submitted.

FDA and sponsors of priority drugs may meet at the earliest stages of clinical testing to plan studies that will help develop the information necessary for a final decision on a product's approvability. Then, when a marketing application is submitted, FDA can mobilize available personnel and other resources needed to review the often large amounts of technical information contained in a priority new drug application.

In another effort to speed the review of marketing applications, the review process is becoming increasingly computerized. New drug applications that commonly run to thousands of pages are now arriving from sponsors in a form suitable for computer processing. This makes review and communication with the sponsor more efficient, saving time for both FDA and the firm.

Accelerated Approval

A highly specialized mechanism for speeding the approval of drugs or biologics that promise significant benefit over existing therapy for serious or life-threatening illnesses—so-called accelerated approval—incorporates several novel elements aimed at making sure that rapid review and approval is balanced by safeguards to protect both the public health and the integrity of the regulatory process itself.

Accelerated review, established by 1991 regulations, can be used in two very special circumstances: when approval is based on evidence of the product's effect on a "surrogate endpoint," and when FDA determines that safe use of a product depends on restricting its distribution or use.

A "surrogate endpoint" is a laboratory finding or physical sign that may not, in itself, be a direct measurement of how a patient feels, functions or survives, but nevertheless is considered likely to predict therapeutic benefit. For example, high blood pressure and elevated serum cholesterol are risk factors for heart and blood vessel disease. Drugs that control blood pressure or cholesterol can reasonably be expected to help control or prevent direct signs of disease, such as angina, congestive heart failure after a heart attack, paralysis following a stroke, and sudden death. Once a drug has been shown effective as measured against such a surrogate endpoint, FDA can grant marketing approval.

As a condition of approval, however, FDA can require the sponsor to carry out postmarketing studies to confirm that the drug does in fact produce a clinical benefit, such as increased survival time. And if further research or experience shows that a product that received accelerated approval cannot safely remain on the market, FDA can order its prompt withdrawal.

As a further safeguard, distribution of accelerated-approval drugs can be limited to institutions that have the capability to use them safely and to physicians with specialized training or experience. The agency can also require that specific medical procedures, such as blood tests, be carried out if they are deemed essential for safe and effective use of the product.

In the summer of 1994, some health professionals and consumers active in the fight against AIDS began expressing concern that drugs in accelerated-approval and expanded access programs (including parallel track and Treatment IND protocols) may be made available with insufficient details about side effects and effectiveness.

FDA convened its Antiviral Drugs Advisory Committee on Sept. 12-13, 1994, as part of a continuing dialogue about expanded access to new HIV drugs.

The review process is becoming increasingly computerized.

Based in part on public testimony and committee recommendations, FDA's antiviral drug division is expected to issue a guidance document for sponsors of AIDS drugs applying for expanded access or accelerated-approval status.

The agency has reaffirmed its commitment to these ways to make new drugs available for people with serious and life-threatening diseases. Working with its advisory committees and other outside experts, FDA will continue to consider improvements to these processes, and implement them where appropriate.

It is clearly too soon to know whether efforts to make drugs and biologics more rapidly and widely available to the desperately ill are contributing to genuine advances in healthcare. But many thousands of patients who might otherwise be beyond hope are now able to seek help from investigational agents, and all of us stand to gain from a more efficient, more responsive system through which to bring important new agents to market.