
SPECIAL ARTICLE

THE REGULATION OF INVESTIGATIONAL DRUGS

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THE search for effective drugs to combat the acquired immunodeficiency syndrome (AIDS) has focused renewed attention on the process by which the U.S. Food and Drug Administration (FDA) regulates the development and availability of new therapeutic agents. The federal government's ability to strike the difficult balance between ensuring the safety of patients and accelerating the availability of new drugs has been seriously questioned. The criticisms persist even though the agency has spent the past 10 years revising its own regulations governing the investigation of new drugs.¹ This article examines the process, including recent revisions, by which the FDA regulates new investigational drugs.

THE REGULATORY PROCESS

Investigational New Drug Application

Before a drug can be studied in humans, its sponsor must submit an Investigational New Drug application (IND) to the FDA.² One of the basic tenets of the

federal drug-regulatory process is that without a sponsor's submission; no clinical investigation will take place — the FDA itself does not investigate new drugs or conduct clinical trials. Pharmaceutical manufacturers, physicians, and other governmental entities, such as the National Institutes of Health, may sponsor INDs.³

Unless notified otherwise, the sponsor may begin to investigate the drug 30 days after the FDA has received the application. The IND review is more like a premarketing notification system — requiring the FDA only to object to unacceptable submissions — than a premarketing approval system requiring it to act on all submissions. In effect, the IND exempts the sponsor from the prohibition against shipping unapproved drugs in interstate commerce and serves as a monitoring device to help the FDA ensure the proper conduct of clinical drug research. The IND requirements extend throughout the period during which a drug is under study.⁴

There are two types of INDs. A commercial IND permits the sponsor to gather the data on clinical safety and effectiveness that are needed for a New Drug Application (NDA), which, if approved by the FDA,

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will allow a drug to be marketed for specific uses. A noncommercial IND allows the sponsor to use the drug in research or early clinical investigation in order to advance scientific knowledge. In 1987, the FD.4 received 302 commercial INDs and 1044 noncommercial INDs.⁴ The agency also distinguishes between INDs in which a person both initiates and conducts a clinical investigation as a "sponsor-investigator" and INDs in which a person or corporation takes responsibility for initiating an investigation as the sponsor, with others (the "investigators") taking responsibility for conducting the investigation.⁵ The two types of INDs have similar requirements. The FDA classifies all submissions according to chemical type and therapeutic potential in order to assign agency review priorities.

An IND allows only the sponsor and the clinical investigators specifically listed in the application to study the drug. With the sponsor's consent, additional investigators can be added through an amendment to the original IND. Other sponsors and investigators who are not listed must submit separate applications with data adequate to meet the requirements of an IND. Data from other applications cannot be used without the express consent of their sponsors. The FDA is prohibited from disclosing or acknowledging the existence of an IND.⁶

In a set of new regulations promulgated in 1987 and known as the "IND rewrite," the phases of clinical study used by the agency since the late 1970s have been defined. Phase 1 includes clinical pharmacology testing in both normal subjects and patients; Phase 2, the first controlled clinical studies of the drug; and Phase 3, expanded clinical trials.⁷ In certain instances, FD.4 approval may be conditional on a fourth phase of postmarketing studies designed to gather additional information about a drug's safety and effectiveness after it is on the market.⁸ The FDA's operating premise is that if successful, Phase 1 should generate enough data to permit a properly controlled trial to be designed for Phase 2. Likewise, at the end of Phase 2, there should be enough data to suggest, if not necessarily prove, that the drug works and to demonstrate its most common adverse effects; and at the end of Phase 3, there should be enough information to establish both the drug's effectiveness for specific indications and the populations at special risk from its use.⁹ Although no firm rules apply, Phase 1 usually involves 20 to 80 patients; Phase 2, several hundred patients; and Phase 3, up to several thousand patients. However, it is the findings obtained in each phase, rather than the number of subjects tested, that form the basis of the decision to proceed to the next phase.¹⁰

Before the IND rewrite, one federal commission studying the process recommended that drug development be regulated through a two-tiered system of classification. In the first stage, basic pharmacologic, toxicologic, and pharmacokinetic information would be gathered, as well as initial data on safety and effective-

ness. In the second stage, the drug's safety and effectiveness would be studied in numbers large enough to provide the evidence necessary to support an NDA.¹¹ Although the FDA has retained the three original phases of investigation in the IND rewrite, it has agreed that in essence, Phase 1 corresponds to an early stage of clinical pharmacology and that Phases 2 and 3 correspond to a later stage of clinical development.⁹ In reality, there is no sharp delineation between the phases. Rather, they represent a progression of clinical research that broadens as it goes on — both in the type of studies pursued, and in the size and heterogeneity of the population tested.⁹

One of the most important aspects of the IND rewrite is that the different phases of the investigational process are regulated differently. In the past, the FDA reviewed all submissions for both the safety and the adequacy of the study design. Under the regulations, the FDA's objective early in drug development is to ensure the safety and rights of subjects; during the later stages the focus is also placed on the study's scientific merit. The FDA's review of submissions in Phase 1 ensures that subjects are not exposed to unreasonable risks. The agency's review of submissions in Phases 2 and 3 also ensures that the scientific design of the study is likely to produce data capable of meeting the requirements for premarket approval of the drug.¹³

By narrowing the focus of the review in Phase 1 to safety, the agency is attempting to reduce "regulatory impediments to scientific creativity" in the early stages of drug development.⁹ Since the vast majority of preliminary drug studies do not lead to marketing applications, the agency has argued that it need not focus on study design so long as human subjects are not put at risk. By broadening the scope of the review in Phases 2 and 3 to include the study design, the agency has attempted to ensure that the later stages of clinical drug research will take place only if the investigation is likely to culminate in drug approval. The importance of evaluating the study design during the course of an investigation rather than at its end — at the time of the NDA submission — is highlighted by a recent study of 68 NDAs showing that a quarter of them were not approved because of flaws in design.¹⁴

All IND submissions must contain information about the drug's chemistry, manufacturing, pharmacology, and toxicology. Data from pharmacologic and toxicologic studies in animals must be sufficient to ensure that a drug is reasonably safe to be used in the proposed clinical studies. Few generalities apply to all new investigational drugs, but toxicologic studies involving two animal species must be performed for at least several weeks before the initial administration in humans.¹⁵ Just as sponsors collect clinical data on humans throughout the investigation, data from animals are also collected throughout the process. By the end of Phase 3, sponsors must collect sufficient information from studies in animals about the potential toxic

effects, both acute and chronic, including **carcinogenicity**, and when appropriate, information about the effects on reproduction and the developing fetus. Ultimately, the amount of data on animals needed to support approval of a new drug depends on the drug's intended use. Drugs intended for short-term use require less testing than those intended for long-term use.¹⁶

If a commercial IND proves successful, the sponsor ordinarily submits an NDA. In 1987, the mean time required for the FDA to approve NDAs for new molecular entities after the date of receipt was 32.4 months.⁴ During this period, the sponsor and the FDA usually negotiate over the adequacy of the clinical data and the wording proposed for the label accompanying the drug, which sets out the indications, effects, dosage, methods and frequency of administration, contraindications, side effects, and precautions. Often, questions about the drug's chemistry and manufacture, rather than about the clinical trials themselves, are the rate-limiting step in gaining approval. A study of 637 NDAs received since 1981 found that the FDA returned two thirds to the sponsor with requests for more information."

In approving an NDA, the FDA must ensure the drug's safety and effectiveness for its intended conditions of use. The safety review of an IND addresses the question of whether there is enough evidence to allow testing to proceed in relatively small numbers of people. In contrast, the safety review of an NDA, whose approval would result in the drug's being marketed, is more detailed. Such a review takes into consideration that many more patients, who are not part of closely monitored clinical trials, will be exposed to the drug. As a result, in the NDA review there is a much closer scrutiny of all the data.

To demonstrate a drug's effectiveness, an NDA must present evidence based on adequate and well-controlled studies rather than expert opinion, isolated case reports, random observations, or clinical experience.¹⁷ Uncontrolled clinical studies can corroborate a drug's effectiveness but are not by themselves a sufficient basis for approval.^{18,19} Although studies to support an NDA must be "adequate and well-controlled," there is no requirement that they always be placebo-controlled. In fact, the agency has stated that the use of placebos is definitely inappropriate in treating life-threatening diseases when an effective therapy is available; in such cases, the clinical trials should compare the test drug with the known effective treatment.^{20,21} The FDA interprets the statutory requirement of "adequate and well-controlled studies" to mean at least two such studies. In contrast, the IND review requires only enough evidence of effectiveness to justify investigating the drug.

The Role of Institutional Review Boards

Since 1971, the FDA has required that all proposed studies be reviewed not only by the agency, but also by an institutional review board. This is a board or com-

mittee that is formally designated by a public or private institution in which research is conducted to review, approve, and monitor research involving human subjects. The composition and function of an institutional review board are subject to FDA regulations." In submitting an IND, the sponsor makes the commitment that each participating clinical investigator will submit all protocols to an institutional review board. The FDA holds the board responsible for the ethical acceptability of the proposed research. The institutional review board must examine the scientific validity of a study to the extent needed to be confident that the study does not expose its subjects to unnecessary risk.*"

Although the responsibilities of the institutional review board overlap with those of the FDA in some respects, there are several areas in which the board's review differs from or complements that of the FDA. First, an institutional review board must formally grant approval before an investigation may proceed, in contrast to the 30-day notification that sponsors must give the FDA. Second, the board must review all informed-consent forms submitted with each protocol. The FDA does not routinely review the consent forms — in fact, they need be submitted only to the review board. Third, institutional review boards must monitor activities within their institutions, since they are likely to become aware of local issues before the FDA does. Furthermore, the agency has generally required that the clinical investigators, not the drug's sponsor, communicate with the institutional review board — an added procedure to ensure that the investigators are included in the review process.²⁴

Monitoring the Safety of Patients

One of the sponsor's most important responsibilities during a clinical study is to report adverse drug experiences to the FDA.' This permits the agency to continue to reassess the risks posed by the study. Similarly, the investigators are responsible for reporting adverse drug experiences to the sponsor and to their institutional review board. In the New Drug Amendments, enacted in 1962, Congress prohibited the FDA from requiring clinical investigators to report directly to the agency.' For the first time ever, the IND rewrite detailed the requirements for reporting adverse drug events while an IND is in effect. The regulations require a sponsor to review promptly all information relating to safety issues that is received from any investigator involved in a clinical investigation, or from any other source, foreign or domestic.²⁵ The sponsor must report any serious and unexpected adverse drug experiences in writing to the agency and all participating investigators within 10 working days. Fatal or immediately life-threatening drug experiences require a telephone report to the agency within three working days.'" The sponsor need not establish a causal relation between the drug and the adverse experience — the regulations require only a reasonable possibility of the drug's having caused the event. Each successive

adverse drug experience of this kind must be reported likewise until the adverse event is either described in the investigator's brochure accompanying the drug or found to be unassociated with the drug's use. Also reportable are any findings of carcinogenicity, teratogenicity, or mutagenicity in studies in animals that suggest a risk to human subjects.²⁷ Reporting of adverse events is also required after a drug has been approved for marketing by the agency.²⁸⁻³⁰ Although product seizure and injunctions are the most common responses to violations of the Food and Drug Act, criminal prosecution is more common in cases characterized by an intentional failure to report adverse drug experiences.

The Treatment IND

The use of investigational drugs is generally limited to subjects enrolled in the clinical studies covered by the IND. For a number of years, the FDA has permitted drugs to be shipped for use by patients who are not part of a controlled clinical trial. Various called "treatment INDs," or "compassionate use" approvals (or "Group C" in the case of the National Cancer Institute), such mechanisms were never formally sanctioned by the agency.³¹ The IND rewrite codifies one type of such use: the treatment IND.³²⁻³⁴ In fact, provisions relating to the treatment IND were the most controversial portion of the IND rewrite.^{35,36} These regulations attempt to make certain investigational new drugs available to desperately ill patients before the FDA approves the drugs for marketing.^{37,38}

The final regulations permit a physician to use an investigational drug in immediately life-threatening and other serious diseases in accordance with a treatment IND if no comparable or satisfactory alternative drug or therapy is available.³⁹ The FDA has defined an "immediately life-threatening disease" as one with a reasonable likelihood either of death within months or of premature death unless immediate treatment is provided.⁴⁰ Examples of life-threatening diseases listed by the agency include advanced AIDS, advanced congestive heart failure, and most advanced metastatic refractory cancers. Examples of serious diseases include Alzheimer's disease, advanced multiple sclerosis, and progressive ankylosing spondylitis.³⁹ To be eligible, the drug must fill a gap in the therapeutic arsenal. Once an alternative therapy becomes available, treatment-IND status is no longer an option.⁴¹ Furthermore, the drug must be under active investigation in adequately enrolled controlled studies or be the subject of completed studies awaiting evaluation and review.⁴² The drug's sponsor must also pursue approval of the drug with due diligence.⁴³ There is a limit to the number of drugs that qualify for treatment INDs, however, simply because there are relatively few drugs that are so uniquely effective in combating life-threatening or other serious diseases. In the first 16 months of the treatment-MD program, the FD.4 approved 7 of 14 treatment-IND proposals.⁴⁴

One controversy that surrounded the use of investigational drugs in treatment concerned the amount of evidence needed for approval of a treatment IND. The proposed regulation stated that the FDA commissioner could deny a request for a treatment IND only if the FDA could establish that the drug provided no therapeutic benefit — a requirement that some have argued would be virtually impossible to satisfy, since such data would not normally exist.⁴⁴⁻⁴⁶ In the final regulations, the FDA permits treatment INDs only for drugs that show some promise of therapeutic benefit. For life-threatening and serious diseases, the levels of evidence required are different. In the case of immediately life-threatening diseases, the FDA requires sufficient scientific evidence to permit experts to conclude reasonably that the drug may be effective — a level of evidence well short of that required for new-drug approval.⁴⁷ In the case of serious diseases, the commissioner may deny a treatment IND if evidence of the drug's safety and effectiveness is insufficient, according to a standard presumably higher than that required to support the drug's use in life-threatening situations.⁴⁸ Whether the agency will actually require different amounts of evidence remains to be seen. The important point is that some data showing potential benefit must be submitted to support a treatment IND.

A decision by the FDA to support a treatment IND is based on a review of the drug's original IND file and not simply the treatment-IND submission. It is unlikely that the agency will approve a treatment IND on the basis of data from uncontrolled studies. In the case of immediately life-threatening diseases, the FDA has suggested that data sufficient to support a treatment IND may be available as early as Phase 2; for serious diseases, sufficient data to support a treatment IND would ordinarily be unavailable before Phase 3.³³ Adequate enrollment in clinical studies is an important prerequisite before the FD.4 permits a treatment IND to proceed. In the end, the decision to approve a treatment IND depends, as does approval of an NDA, on the judgment of the FDA reviewers, who take into account the disease, the alternatives, and the available evidence.⁴⁹

A major concern about the availability of treatment INDs is their potential effect on the integrity of ongoing clinical trials whose enrollment they may undercut.⁵⁰ If patients who participate in clinical trials no longer agree to be randomly assigned to treatment and control groups once a drug is available under a treatment IND, the clinical trials may be compromised.⁵¹ Ethical issues will undoubtedly arise for the physician caring for patients enrolled in such studies. According to some at the FDA, the existence of the treatment IND in itself does not create the ethical dilemma — instead, the issue is how much information is needed before a randomized clinical trial should be terminated.⁹

As with any other IND, a drug company, an individual physician, or an entity such as the National

Institutes of Health may sponsor a treatment IND. The requirement that the sponsor determine the qualifications of those who will administer the drug also applies to a treatment IND.³⁹ Depending on the situation, qualifications may range from being a licensed physician to possessing specialized expertise or subspecialty training.

The aspect of the FDA's new regulations that deviates the most from past practice is the set of rules allowing manufacturers to charge for investigational drugs, especially treatment INDs.^{39,51} FDA rules create the presumption that IND research is a part of the cost of doing business, permitting cost recovery from IND studies other than treatment INDs only if the sponsor can show that recovery of costs is necessary to the undertaking of the clinical trial." By contrast, the new FDA regulations create a presumption favoring cost recovery under a treatment IND to encourage manufacturers to make potentially lifesaving drugs available before they receive NDA approval, especially since such use is not considered to be included in the cost of doing research." After notifying the FDA, sponsors are permitted to recover costs as long as the charges do not constitute commercialization by exceeding the costs. Furthermore, sponsors must not promote or advertise the drug commercially.

"Compassionate Use" Approval

The treatment IND does not cover all instances in which a physician may need to use an investigational drug to treat patients. They may still need to seek approval on a "compassionate use" basis, for example, when no IND is in effect for a drug that is being investigated or marketed abroad. A treatment IND will not be approved in such a case because no IND is in effect. Or a physician may need "compassionate use" approval to use a drug for purposes not described in the IND protocol. Treatment INDs are available only for drugs well along in the testing process and for which there is a considerable amount of data. In special circumstances physicians may want to have drugs that are not so far along in their development shipped to them for use by certain patients. In all such cases, the physician must contact the review division of the FDA that is responsible for the drug or disease in question.³³

Most recently, in response to the requests of a number of patients with AIDS who wished to import dextran sulfate, an unapproved drug that some believe may be useful in treating AIDS, the FDA announced that it would permit patients to import small quantities of unapproved drugs from foreign countries on a pilot basis, in the absence of evidence of unreasonable risk or fraud.^{54,55} The safety and effectiveness of such agents need not be established, but such imports are limited to personal use. No commercial distribution or promotion is permitted, and patients must supply the name of a physician who will be responsible for their treatment. The FDA continues to detain products that may appear fraudulent or dangerous. Earlier restric-

tions remain in effect on such drugs as Laetrile and immunoaugmentative agents.

The new import policy can be viewed as an extension of the FDA's longstanding compassionate-use policy. Invoking its enforcement discretion, the agency has often ignored small amounts of unapproved drugs brought into the United States for personal use by persons returning from trips abroad. The new policy goes one step further by allowing such imports to be mailed. By articulating the new policy, the agency has, in a limited fashion, confronted publicly a question that has long plagued it: Do patients who suffer from life-threatening disorders for which there is no treatment have a right to take unproved remedies?⁵⁶ To the extent that the policy permits fraud, interferes with the development of other agents, or exposes patients to unsafe medications, it will fail to protect those whom it was designed to help. To the extent that it allows patients some control over their care and the FDA takes the initiative to ensure that they are properly informed about the value of the therapy they receive, the policy fulfills an important need.

Unapproved Uses of Approved Drugs

The FDA assesses the safety and effectiveness of drugs with specific reference to their intended use, as described on the label. A manufacturer who ships a drug in interstate commerce intending that it will be used for purposes beyond those stated on the label is in violation of the Food and Drug Act." What happens, however, if a physician prescribes a drug for an unapproved use without the shipper's knowledge?⁵⁸ Precisely when a physician is required to file an IND before prescribing an approved drug for unapproved uses was not clearly addressed by the agency until the new regulations were issued.⁹ In enacting the nation's drug laws, Congress attempted to steer away from regulating the practice of medicine. Thus, a physician may treat patients with an approved drug for indications not included on the drug's approved label, subject to possible malpractice action.⁵⁹ According to the new FDA regulations, a different issue arises if a physician uses a drug not to treat but to investigate an unapproved use of an approved drug. Under the new regulations, investigations of the use of approved drugs differing from the approved use only in doses, routes of administration, or types of population treated are exempt from IND requirements if two conditions are met: if the investigation does not substantially increase the associated risks, and if the sponsor does not intend to present the data to the FDA in support of new uses or changes in the drug's approved labeling or promotional materials.⁶⁰ Even if they are exempt, such investigations are subject to the agency's requirements for an institutional review board and informed consent, as well as to the general prohibition against the commercialization and promotion of unapproved products. The FDA's newly articulated policy permitting physicians to explore certain new uses of approved drugs without submitting an IND, so long as

major safety questions are not raised, is consistent with the agency's goal of reducing the administrative burdens of early research.

DISCUSSION

The FDA has been severely criticized for intransigence in the face of the AIDS epidemic.⁶¹ Its critics argue that the process of developing and approving new agents has taken too long, that the agency has not made potential agents available, and that it has made the investigation of such agents inordinately difficult for physicians.

On analysis, it is important to recognize that the FDA could easily accelerate the availability of new drugs. Likewise, it could provide greater assurances that drugs reaching the market are safe and effective. Neither goal alone is sufficient, however. The agency's job is to balance the need to make drugs available quickly with the need to ensure that patients do not receive unsafe or ineffective products. Since it cannot pursue any single objective, criticism can always be leveled against the FDA from either direction. Nevertheless, when there is no alternative treatment for a life-threatening disease, greater emphasis may need to be placed on accelerating development than on ensuring every aspect of safety and effectiveness. Not only does the risk-benefit equation permit the acceptance of greater known risks in the light of greater known benefits, it also permits decisions to be made on the basis of fewer data, with more unknowns, in instances when a life-saving drug has a demonstrable benefit.

Balancing conflicting goals is difficult, but each aspect of the approval system must be examined to determine whether drug development can be accelerated without vitiating assurances of safety and effectiveness. The first question that requires examination is whether the FDA needs to be as involved as it is in the investigational stages of drug development. In West Germany, by comparison, there is limited government regulation during early clinical research.⁶²

Few would wish to see the FDA's oversight of clinical drug investigations eliminated, but in the new regulations the agency has sought to reduce its regulatory control in the early phases. Furthermore, for the past several years it has been discussing the merits of giving local institutional review boards more responsibility for reviewing early clinical studies.⁷ The agency has considered, but has not adopted, a "dual track" whereby sponsors could choose to have their Phase I studies reviewed by a third-party nongovernmental body instead of the FDA. According to such proposals, the responsibility for scientific and ethical review would be delegated.⁶³ There is little support, however, for the delegation of responsibility for early investigations to all local institutional review boards. Two major considerations account for this view. First, such boards generally lack specific toxicologic, pharmacologic, and chemical expertise. Second, local boards are unwilling to handle the liability issues associated with approving the use of investigational drugs.¹³ More-

over, in the case of a multicenter study, it would be redundant for more than one institutional review board to review toxicologic, pharmacologic, and chemical data, since local issues are usually not involved in these aspects of the study.⁶⁴ Instead of having all institutional review boards assume responsibility for review, the FDA has stated that it would consider establishing demonstration projects whereby a willing and expanded institutional review board or some other nongovernmental body could assume such responsibility.¹³ Nevertheless, earlier rather than later FDA involvement may be an important factor in accelerating the review process.

The second question that requires examination is whether the standards for safety and effectiveness — those set either by Congress in the statute or by the agency in its regulations — are appropriate. There are several different standards governing the approval of INDs and NDAs. During the early phases of an IND, the standard requires that the safety of subjects be ensured; during the later stages it also requires a sound study design. Treatment INDs require the presentation of sufficient evidence for the FDA to conclude reasonably that the drug in question is effective. An NDA requires adequate, well-controlled studies. The more widespread the intended use of the drug, the stricter the FDA's requirements. There has been some suggestion that a mechanism for conditional approval should be created, especially for breakthrough drugs.^{65,66} Under such a mechanism, the standard of effectiveness would be less rigorous than that used in NDA approval, but approval would be conditional on further testing in Phase 4 and surveillance after the drug is on the market. The treatment IND and the suggested conditional approval have similar goals. Both permit the FDA to require additional studies after the drug has been made more widely available. To the extent that the treatment-IND program makes major new therapies widely available to patients with life-threatening diseases, the need for a mechanism of conditional approval is limited. To the extent that the treatment IND remains a difficult maze for patients and physicians to navigate, conditional approval may be a valuable means of ensuring that patients have early access to important new agents.

A third matter for examination has to do not with the standards themselves, but with what can serve as a sufficient basis for meeting them. The standards are legal requirements, and the evidence is scientific data; there is no such thing as a perfect match between the two. Although the same legal standard for drug approval that applied in 1962 still obtains, few NDAs that were approved in 1962, if any, would be approved now on the basis of the same information.²⁴ There is a perception that the criteria for NDA approval resemble a moving target. Since all clinical investigations are characterized by imperfection in some degree, the FDA can always request more evidence or raise additional questions about a study. It has been argued that

FDA reviewers sometimes focus on "deviations from technical requirements" rather than on whether "despite the deficiencies, the study provides reliable scientific evidence of the drug's effectiveness."⁶⁷ To some, NDAs are sometimes judged against "inflexible, preconceived criteria regarding study design."⁶⁸ On the other hand, part of the reason for the perception is that the FDA's base of scientific knowledge is also expanding in the areas of pharmacology, toxicology, and therapeutics. Even if extreme care has been taken to address all major issues at the outset of a study, new issues will undoubtedly arise by the conclusion. Ultimately, the decision about whether the results of a clinical investigation are adequate and well controlled rests with the judgment of the FDA reviewers. The FDA's IND rewrite improves communication between the sponsor and the agency by mandating meetings at the end of Phase 2 and before the NDA is submitted, with the goal of establishing early in the investigation what the agency will require before granting approval.⁶⁷ More recently, the agency has instituted a process for holding conferences at the end of Phase 1, or even before the submission of the IND, with the sponsors of drugs and biologic agents that are intended for use in life-threatening diseases.⁶⁸

Probably the most important lesson on how to accelerate the approval of important new drugs has come from the FDA's experience with zidovudine (formerly called azidothymidine, or AZT).⁶⁹ Only two years elapsed after the first observation of the drug's activity against the human immunodeficiency virus in vitro before it was made available to treat patients." Although the approval of zidovudine is not representative of the process by which the vast majority of investigational drugs are approved, it is because of precisely such differences that important lessons can be learned. In the case of zidovudine, one multicenter, Phase 2, double-blind, randomized, placebo-controlled study involving only several hundred patients satisfied the agency's requirement for an adequate, well-controlled study. No Phase 3 studies were required. Toxicologic testing was far from complete. The reason the FDA accepted the single trial as sufficient was that it incontrovertibly supported the drug's efficacy. The agency's focus on the adequacy of data to demonstrate safety and efficacy rather than on the completion of all phases is an important lesson to be learned from the approval of zidovudine.

Instead of altering the existing system of drug approval, many of those involved in drug regulation believe the process could be compressed to accommodate important new drugs. The FDA has recently issued interim regulatory procedures that recognize that well-designed, somewhat larger, more extensive, multicenter Phase 2 studies that produce meaningful, reliable, and consistent data should be able to support a decision by the agency to make a breakthrough drug more widely available.^{21,71-76} Some elements of Phase

3 trials, such as the study of different doses, could be incorporated into such larger Phase 2 trials." Other issues normally addressed in later clinical trials — the optimal dose, the optimal dose interval, the optimal duration of therapy, the profile of long-term adverse drug events, and the need for testing in special populations and circumstances — may have to be addressed after the drug is initially made available. One note of caution is in order. The Phase 2 data on zidovudine were highly persuasive. How generalizable the zidovudine model is to other important new agents remains to be seen.

In any case, as the regulation of zidovudine demonstrates, the FDA's involvement with IND sponsors early in the process is critically important to the expeditious approval of important drugs. In the vast majority of cases, the agency does not focus much attention on the drug until the NDA is submitted, when all the data collected during the investigational phases are analyzed and submitted. The FDA's involvement throughout the development of zidovudine consumed major agency resources. Furthermore, at the time, zidovudine was one of the few INDs that was being pursued for the treatment of AIDS; now several hundred INDs are being pursued for treatment of this disease.^{78,79} Only by focusing as much attention on them as it did on zidovudine will the agency be able to accelerate the approval of other AIDS drugs. And as important as early involvement is to accelerated drug approval, so is the agency's role in the process, not only as regulator, but also as facilitator of the development of new drugs.

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