Drug Regulation and Policy Formulation

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IN ORDER TO EXPLAIN SOME OF THE CURRENT issues in the policies governing the regulation of clinical investigations and the approval of new drugs, it will be helpful to review briefly the legislative basis for such regulation. This paper will identify the major legislation that Congress has passed in the drug area during this century and summarize the basic policies that they reflected. Then some of the major regulations rooted in that legislation will be identified, and, finally, other efforts (e.g., guidelines) that represent the Food and Drug Administration's (FDA) implementation of the policies embodied in the legislation will be noted. This discussion will lead toward a review of proposed and current administrative and regulatory changes that reflect important policy considerations before FDA.

This paper will concentrate on issues in drug research, particularly concerns about human subject protection and validation of research data. Also, current problems and proposals that involve certain larger societal issues will be discussed, including the therapeutic use of investigational drugs; state drug-specific legislation (marijuana, lae-

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trile); the so-called drug lag; what are popularly known as "orphan drugs"; and international issues.

The Current Process

Legislative Basis for Drug Regulation

The first federal act regulating drugs was the Pure Food and Drug Act of 1906. This act was geared to correct the widespread promotion and unrestricted sale of patent medicines containing drugs such as opium, heroin, and cocaine, as well as the failure to indicate the presence of these dangerous substances on the medicines' labels. Also, relatively innocuous preparations were labeled and promoted as curing every disease and symptom. Not only did labels not list ingredients, but warnings against misuse were nonexistent (Janssen, 1979).

The act stated that drugs were to be deemed adulterated if they were sold under or by a name recognized in the official compendia but failed to meet compendial standards. An exception was provided: a drug using a recognized name that did not meet the official standard would not be deemed adulterated if it met its own standard of strength, quality, and purity, which had to be stated plainly on the bottle, box, or other container. Any drug that failed to meet the professed standard under which it was sold would, however, be deemed adulterated. The 1906 act declared that a drug was deemed misbranded if its label bore any statement or design regarding the contents that was false or misleading, or if the drug was falsely branded as to the state, territory, or country in which it was manufactured. Moreover, drugs would be misbranded if they were an imitation of, or were offered for sale under the name of, another article (false name) or if the original contents had been removed in whole or in part and other contents added (false contents). Drugs would also be misbranded if their labels failed to indicate any quantities of alcohol, narcotics, and certain other specified substances present in the product (House of Representatives, 1974).

In 1938, Congress repealed the 1906 act in favor of the federal Food, Drug, and Cosmetic (FD&C) Act. That legislation was motivated in part by the "elixir of sulfanilamide" disaster. In an effort

to prevent another such tragedy, the act of 1938 provided for premarket clearance of new drugs to ensure safety. Before marketing, manufacturers were required to submit to FDA full reports of investigations that had been undertaken to establish safety. Unless the FDA, within a specified period of time, issued an order finding that safety had not been established, the manufacturer could proceed to market the drug. The FDA was also authorized to exert regulatory authority beyond the initial stages of drug development. The act permitted FDA to remove from the market any drug that it subsequently could prove unsafe. Old drugs already on the market were not subject to these requirements, however. They were allowed to remain on the market unless FDA could prove in court that they were dangerous.

It is important to note that the 1938 act did not require a drug to be proved effective as well as safe in order to be cleared for marketing. But in making its judgments about safety, FDA did consider effectiveness. The relationship between safety and effectiveness is considered elsewhere. It is sufficient to note here that, according to the 1938 act, the manufacturer of a product did not have to prove that the product did what it was reputed to do (House of Representatives, 1974).

In 1962, following the Thalidomide episode, Congress strengthened the new drug clearance procedure and gave FDA more control over drugs used in investigations through passage of the Kefauver-Harris drug amendments. With thousands of physicians prescribing Thalidomide to their patients under the guise of research, Congress was forced to recognize that the 1938 act did not require that FDA be notified if a drug were being tested in humans. Congress also recognized that no drug could be considered truly safe unless it were also effective. Thus, the New Drug amendments of 1962 required, for the first time, that drug manufacturers prove their products *effective* as well as safe before marketing. Whereas the 1938 statute demanded that the manufacturer prove only the safety of the product, the 1962 amendments required the manufacturer to demonstrate both safety and effectiveness.

The terms "effectiveness" and "efficacy" have been treated frequently as synonymous in references to the requirement for drug approval mandated by the New Drug amendments of 1962. Some commen-

tators draw a distinction in their meanings. A report published in August 1980 by the Office of Technology Assessment (OTA) of the U.S. Congress defines efficacy as: "The probability of benefit to individuals in a defined population from a medical technology applied for a given medical problem under ideal conditions of use" (U.S. Congress, 1980). The FDA is moving away from the use of the term efficacy to avoid ambiguity and to make explicit the fact that drugs are approved and labeled for use under the general conditions of medical practice, not the more idealized conditions often found in investigational settings.

Additionally, the 1962 New Drug amendments require that drug companies send adverse reaction reports to FDA and that drug advertisements in medical journals provide complete information for physicians on the risks as well as the benefits of marketed drugs.

Under the 1962 amendments, before human testing can begin, a sponsor must submit an application that identifies to FDA complete information about the drug, its composition, source, method of manufacture, and how it is intended to be used in patients. Also, the results of preclinical studies, including animal studies, must show that it is reasonably safe to begin human studies. The sponsor must wait 30 days before initiating clinical studies so that FDA can review the submission.

Before 1962, the manufacturer was not obligated to report any information on adverse findings that would cast doubt on or disprove the safety of the product after it was introduced into the market. The 1962 amendments require the manufacturer to keep FDA advised of adverse experiences and other data that would shed light on the status of the manufacturer's product in general use.

An important feature of the 1962 amendments was the provision that enabled the Food and Drug Administration to require tests of effectiveness for every product that was subject to the new drug provisions of the 1938 act. In short, a review of effectiveness—which is now, in 1981, almost completed—was mandated for every new drug introduced between 1938 and 1962 (House of Representatives, 1974).

Although there has been no major new drug legislation enacted since 1962, the administration transmitted the Drug Regulation Reform Act of 1978 to Congress in that year (and resubmitted it in

1979). Over the past several years, a number of congressional hearings on specific bills and major issues in drug regulation have been held. The provisions of these bills deal with the important policy issues before FDA and will be discussed later.

Regulatory/Administrative Basis for Drug Regulation

Legislation requires FDA to issue regulations explaining and detailing requirements in the law and to provide guidance to industry and consumers about what must be done to ensure acceptable products and to comply with the law and regulations themselves. Federal legislation—laws enacted by the Congress and approved by the president (or passed over a presidential veto)—frequently sets broad objectives and procedures, the specific and detailed application of which are to be established through federal regulations promulgated by a named federal official. FDA regulations, issued under a delegation of authority from the secretary of health and human services (HHS) to the commissioner of food and drugs, customarily originate as proposals published in the *Federal Register* to elicit public comment; public hearings often are held for the same purpose. The commissioner, after giving due consideration to written and, if there is a hearing, oral comments on a proposed regulation, issues a final regulation, which has the force of law and may be challenged in the federal courts. The drug amendments of 1962 required for the first time that FDA issue Good Manufacturing Practice regulations (enumerating procedures to ensure the production of safe, *effective* drugs) as well as regulations governing investigational drugs and the conduct of clinical investigations. Such regulations are codified in the *Code of Federal Regulations* (Title 21), which is revised and published annually. Clinical investigators are governed by these latter regulations, which were first promulgated in their current form in 1974. Investigators must sign forms enumerating their responsibilities. However, in 1978, FDA proposed specific regulations governing the conduct of clinical investigators themselves. These proposals, not yet published as final regulations, emphasize issues of human subject protection and validity of data. Furthermore, they characterize in some detail issues that were

either not addressed fully or not dealt with in the current regulations with respect to clinical investigators.

For various reasons, major portions of the Investigational New Drug (IND) and New Drug Application (NDA) regulations are now considered to be outdated or, at least, to lack the specificity needed to protect human subjects or ensure that valid data are being collected. To a great extent, proposed or already final regulations published under the auspices of other federal agencies—the National Institutes of Health (NIH)—or under other FDA programs (e.g., bioresearch monitoring programs, medical devices, etc.) have highlighted the need for revisions of the basic IND and NDA regulations. A "concept" document published by FDA's Bureau of Drugs in October 1979 (Department of Health, Education, and Welfare, 1979a) incorporates references and approaches to much of this other regulatory activity and proposes revisions in current regulations. This revision is necessary because FDA's internal process for evaluating new drugs has continuously evolved over the years, becoming more complex, while formal regulations have been revised only infrequently, generally to deal with specific concerns.

New Drug Regulations (NDA Process). Approximately 90 percent of the drugs marketed since the Food, Drug, and Cosmetic Act was passed in 1938 are "new" drugs in a medical and legal sense; thus, the principal system of controlling drugs in the United States is the NDA process. The NDA requirements are spelled out in section 505 of the federal FD&C Act (U.S. Congress, 1980a). The law requires that before a new drug may enter interstate commerce it must be the subject of an approved NDA, requirements for which appear in the *Code of Federal Regulations* (Code 314). This NDA requires the demonstration of safety and effectiveness as detailed in these regulations.

All drugs that are considered "new drugs" must be demonstrated to be effective before they can be marketed in interstate commerce in the United States, or be imported or exported. Since the approval of an NDA establishes safety and effectiveness for a particular indication (or indications) of use of a drug and allows interstate commerce, the latter becomes critical to the sponsor, who is usually, but not always, the manufacturer.

Drugs that fit the definition of "new" include: a drug containing a newly developed chemical—or a chemical or substance not previously

used in medicine; a drug previously used in medicine but not in the dosage or condition for which the manfuacturer now recommends its use; or a drug recognized by qualified experts as safe and effective for its intended uses as a result of investigational studies, but not otherwise used to a material extent or for a material time (Department of Health, Education, and Welfare, 1979b). Specifically, a new drug is defined by Section 201 of the act (U.S. Congress, 1980a) as any drug not generally recognized, among qualified experts, as safe and effective for use under the conditions prescribed, recommended, or suggested in the drug's labeling. A new drug may be an entirely new substance, a marketed drug in a new formulation, or a marketed drug being proposed for a new use, that is, a use for which the drug is not already approved.

The other 10 percent of drugs that are not "new drugs" are those that are generally recognized by experts as safe and effective because of their long marketing history ("grandfathered" drugs).

The development of new drugs usually begins with the screening of chemical compounds in laboratory animals for possible therapeutic activity. The most promising compounds are selected for further study. The safety and effectiveness of a new drug product must be demonstrated through closely controlled clinical tests. After completing animal and clinical tests, the sponsor may file with FDA a new drug application (NDA), which, if approved, permits the sponsor to market the drug. The NDA includes: 1) full reports of investigations, including animal and clinical investigations that have been made to show whether the drug is safe and effective; 2) a statement of the drug's composition; 3) a description of the methods used in, and the facilities and controls for, the manufacturing, processing, and packaging of the drug; 4) samples of the drug and components as may be required; and 5) a copy of the proposed labeling.

Detailed requirements, delineated in regulation and law, emphasize the need for acceptable scientific data, including the results of tests, to establish safety and substantial evidence of effectiveness in the conditions in which the drug is to be used. The law defines substantial evidence as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could be fairly and responsibly

concluded by such experts that the drug will have the effect it purports to or is represented to have under the conditions of use prescribed, recommended, or suggested in, the labeling thereof" (U.S. Congress, 1980a, 505d).

Investigational Drug Regulations. Investigational drugs are new, unapproved drugs intended solely for investigational use by experts qualified by scientific training and experience to study the safety and effectiveness of drugs (U.S. Congress, 1980a, 505i). Such drugs can be distributed in the United States and can even be imported, but the distribution can be only for investigational use and can take place only after an acceptable "Notice of Claimed Exemption for a New Drug" (IND) has been filed with FDA by the sponsor. In order to file successfully for an IND, the regulations (Code 312) that describe the process must be followed (General Services Administration, 1980). These regulations govern the information on the planned research protocol, specifics about the drug to be tested, and the qualifications of the clinical investigators.

Guidelines for Clinical Investigations and Other Aspects of the Drug Approval Process. Although not strictly regulatory, FDA has published companion guidelines to existing drug regulations, beginning with the publication of a series of guidelines for testing specific classes of drugs in human subjects. To date, FDA has published twenty-three of these on various drug classes, as well as one on manufacturing and controls, and is in the process of developing guidelines for animal testing (Department of Health, Education, and Welfare, 1980). This series was initiated in response to concerns by drug sponsors and investigators about a lack of guidance on studies needed for different classes of investigational drugs at different stages of their testing. There was also some confusion over the definitions of the three designated phases (see below) of clinical investigations. Formalization of guidance in this manner has been salutory because it minimizes discrepancies between what FDA requires to establish safety and effectiveness for any particular type of drug and what sponsors and investigators believe is needed at various phases in the investigational process for different classes of drugs.

These guidelines were developed through the collaboration of outside advisory committees composed of expert consultants with, in some cases, the collaboration of medical specialty groups. In all cases,

FDA staff members participate in and coordinate these activities. No guideline is published, however, unless it gains the approval of the advisory committee primarily responsible for its development.

Legislative and Administrative Proposals on New Drug Development and Clinical Investigations

Legislation: Drug Regulation Reform Act

During the 96th Congress, two legislative proposals entitled the Drug Regulation Reform (DRR) Act of 1979 (H.R. 4258 and S. 1075) were introduced. Each proposal would have made substantial changes in FDA's statutory authority for the regulation of drugs. H.R. 4258 (the administration-sponsored bill) would have completely revised the 1938 FD&C Act, whereas S. 1075 would have retained certain provisions of the original act, modified some provisions, and added provisions to make the drug approval process more efficient and effective. Neither bill received final congressional action before the close of the 96th Congress. Similar legislation has not been introduced in the 97th Congress. The following discussion presents a brief history of recent interest in legislative reform and the rationale for various proposals.

The history of S. 1075 began in 1967 when the Monopoly Subcommittee of the Senate Select Committee on Small Business, chaired by Senator Nelson, commenced a series of thirty-nine public hearings over 150 days on various aspects of the pharmaceutical industry: drug development and marketing; drug quality, safety, and effectiveness; effects of promotion and advertising; bioequivalence and bioavailability; promotion of prescription drugs in Latin America; and the pharmaceutical industry's impact on medical education. In 1973, the Health Subcommittee of the Senate Labor and Public Welfare Committee, chaired by Senator Kennedy, also began to examine the system under which drugs are approved and used in the United States. The Health Subcommittee held over 35 days of public hearings between 1973 and 1978 (Senate, 1979). Other Senate hearings on the DRR Act of 1979 and a related bill were held in the spring of 1979.

In response to questions raised during earlier hearings, in February 1975 the secretary of HEW established the Review Panel on New Drug Regulation, chaired by Norman Dorsen of the New York University School of Law. The secretary charged the "Dorsen Panel" to study current policies and procedures of FDA relating to the review of new drugs.

The panel issued a comprehensive report of its findings and recommendations on May 31, 1977 (Dorsen, 1979). Its principal conclusions were: 1) the system of new drug regulation that requires premarket clearance of prescription drugs, based on evidence of safety and effectiveness, is fundamentally sound; 2) FDA is neither pro- nor anti-industry in its review and approval of new drugs; and 3) FDA's implementation of the system of drug regulation needs substantial improvement.

The panel found four major areas in which improvements were necessary. These related to increasing FDA's scientific capabilities, making the drug review process more open and accountable to the public, improving the standards and procedures for premarketing approval of new drugs, and increasing FDA's authority in the postmarketing period. Many of the panel's recommendations were reflected in the DRR act of 1979, S. 1075 (Senate, 1979).

The following discussion of the provisions of the legislation proposed in the last Congress is excerpted from various FDA publications, a report by the Comptroller General, and congressional committee reports.

Phases of Clinical Investigations. Under the current system, a new drug that has promise for successfully treating human illness is first tested in animals. If the animal tests disclose no toxic effects and indicate probable therapeutic benefits, the manufacturer may submit an IND to FDA for review. If the FDA finds the IND acceptable, the manufacturer may begin tests on human subjects. Such clinical tests are conducted in three phases. Phase I trials involve a small number of healthy persons and a few patients for whom the investigational drug is assumed to be potentially beneficial. These trials are conducted under rigorously controlled conditions by persons trained in clinical pharmacology. Their primary purpose is to assess mechanisms of action and to lay the groundwork for development of protocols to be followed in subsequent clinical investigations. Phase II testing again involves limited numbers of patients whose condition

may be expected to benefit from the use of the drug. These trials are concerned with both the safety and the effectiveness of the agent in carefully controlled experimental regimens. Phase III studies are conducted in as many as 3,000 or more patients whose exposure to the drug approximates conditions that would be encountered in general use of the product. A drug that reaches this stage of clinical testing and is found to be safe and effective is likely to be approvable. Most investigational drugs, about 90 percent, do not go beyond the first two testing phases because they do not show enough therapeutic promise.

The proposed legislation set forth a number of changes in the current process. Three distinct categories of clinical studies would be created:

1. Drug innovation investigations involving small numbers of healthy subjects and patients, intended to examine the clinical pharmacology of a drug, make preliminary assessments of its risks and effectiveness, or determine its biological mechanisms in man.
2. Drug development investigations to evaluate risks and effectiveness.
3. Drug treatment investigations allowing the use of a drug on a small number of humans who, having a serious disease or condition, small number of humans who, having a serious disease or condition, cannot be satisfactorily treated by other forms of therapy. This use of drugs is intended to provide treatment rather than to assess risks of effectiveness.

The general objectives of these sections of the administration's bill included protecting the rights and health of humans who participate in clinical investigations and establishing procedures to ensure that clinical investigations are conducted as promptly as possible with as little FDA review and oversight as necessary. It is expected that reducing regulation during the investigational period would encourage drug innovation.

Breakthrough Drugs. Provisional approval of breakthrough drugs would permit these drugs to be used sooner than they would become available under the current drug approval process. The breakthrough provision was intended to apply to a small number of drugs that clearly represent potential major therapeutic advances on the basis of evidence that is less than the statutory standards. The significance

of the provision was its benefit to patients from the early release of the drugs.

Under current legislation, FDA cannot approve any drug for marketing if it finds that certain deficiencies exist with respect to the contended safety and effectiveness of the drug, including the lack of substantial evidence of the drug's effectiveness. Under the proposed legislation, certain potentially valuable drugs would have been permitted on the market if specific conditions were met, including the following: the drug is intended for use in life-threatening or severely debilitating illness or injury; the drug constitutes a major therapeutic advance; delaying its approval would pose significantly greater risks to patients than would immediate provisional approval; there is significant but not substantial evidence of the drug's effectiveness; and well-controlled tests are, if ethically and methodologically possible, under way.

A drug that meets these conditions would be classified as a "breakthrough drug" and would receive provisional approval for three years. Approval would be renewable if tests were still underway and all of the above conditions continued to be met.

The proposed authority for breakthrough drugs was planned to accelerate the approval of drugs thought to be major therapeutic advances without opening a loophole for provisional approval of unsafe, ineffective, or unnecessary new drugs. The proposed authority would not have compromised the safety of the drug since the secretary of HHS would have had to make a risk-benefit assessment similar to that made for all drugs before FDA approval. The secretary would have less evidence of effectiveness, but the evidence would have to be sufficient to demonstrate that the benefits of the drug outweigh the risks and that the drug offers major therapeutic advantages for patients with life-threatening or severely debilitating illness or injury.

Restricted Distribution. The administration's bill would also have permitted restricted distribution of certain drugs to a controlled environment, rather than general distribution, because of the risk associated with them. For example, the drug might be used only under carefully controlled circumstances, such as in a hospital.

Such conditions were to be placed on drugs only if certain circumstances obtained: the risk of the drug product was so significant that the drug could not be determined safe unless the restrictions were imposed; the imposition of such restrictions could reasonably be ex-

pected to reduce the identified risk sufficiently to permit such a drug to be considered safe and effective; and no other administrative or educational action could reasonably be expected to reduce such risk to an acceptable level.

In addition, before any conditions could be placed on the drug's distribution, the opinion of an advisory committee would have to be obtained. Furthermore, no conditions on the use of a drug by experienced practitioners in certain facilities, such as hospitals, could be imposed unless it were determined that such conditions were necessary for the drug to be considered safe.

Postmarketing Drug Surveillance. Improved postmarketing surveillance of drug use and experience is needed to provide information to determine whether further regulatory action should be taken with respect to an approved drug. When use of a drug by patients increases after approval, unexpected adverse effects may appear. Hence, a primary purpose of postmarketing surveillance is to identify those effects and assess their significance.

The administration's drug regulation reform proposal would have required drug manufacturers to establish and maintain a system for collecting and reporting adverse drug reaction information to FDA. This postmarketing surveillance was intended to monitor the use of a marketed drug to compile data on uncommon adverse reactions that may or may not have been detected in clinical trials. This requirement would have been imposed where it was judged necessary or useful in evaluating the continuing safety of a drug.

Administrative Proposals and Activities: IND/NDA Rewrite and Bioresearch Monitoring Program

Rather than merely wait for enactment of new legislation—because such reform is necessary now—the FDA is moving in many areas within its current legislative authority to streamline the drug approval process and encourage innovation, while at the same time continuing to protect human test subjects and the public health in general. Two of the more significant of these initiatives are discussed below.

IND/NDA Rewrite. In February 1979, the commissioner of food and drugs approved a proposal to revise the investigational and new drug application (IND/NDA) regulations. A concept document, "Investigational and New Drug Regulations Revisions," developed by

the Bureau of Drugs and published in October 1979 (Department of Health, Education, and Welfare, 1979a), was the topic of a public meeting held in Washington, D.C., on November 7, 1979. Approximately 170 persons representing more than sixty pharmaceutical companies, several hospitals, and independent researchers and consultants attended the hearing. Following that meeting, FDA began the process of drafting revisions to the IND/NDA regulations. Current plans are to publish these in a revised form during 1981 as a proposal for public comment.

The following specific provisions in the initial rewrite concept paper were proposed to facilitate a more efficient review of INDs and NDAs:

1. Better organization of data submitted to FDA (i.e., revisions in the format and nature of data submission).
2. Submission of copies of all published articles important in FDA's review, as opposed to the current practice of merely referencing some of this material in the application.
3. Allowing certain changes in an approved NDA without prior approval by FDA, thus reducing some of the agency's workload without compromising public safety.
4. Reduction in the periodic reporting burden on applicants (i.e., at three-month and six-month intervals following NDA approval). The proposal would require only annual reporting following NDA approval, except for serious or unexpected adverse reactions which must be reported promptly.

The FDA intends to provide guidelines relating to various portions of the revised IND/NDA regulations. Such guidelines for content and format should facilitate the review process by assisting applicants (sponsors) in their understanding of the requirements. Guidelines under development include instructions on: preparation of IND forms as revised; preparation of IND annual reports and comprehensive summaries; preparation of NDA submissions and annual report forms; and format for submission of data and preparation of adverse reaction forms. Guidelines defining adequate data to assure bioavailability and bioavailability requirements are also planned. Several specific examples of the issues dealt with are as follows:

Whereas current regulations require adequate controls to be used in clinical trials, the concept paper proposes regulations that would set forth a hierarchy (most to least desirable) of types of controlled

studies, reflecting their scientific merit, as follows: placebo control, no treatment control or active treatment control, and historical control.

The concept document's discussion of this proposal emphasizes that such a hierarchy does not imply that only placebo-controlled studies are acceptable; there are many situations in which such a study would be intolerable on ethical grounds. It would mean, however, that the placebo control is presumed to be the design of choice unless there is good reason not to use it. A person who proposed a different design would need to explain why a placebo-controlled study was unnecessary or inappropriate and how an alternative design would be satisfactory.

Another area dealt with in the concept paper is the "treatment IND." The regulations would specifically recognize the concept of a treatment IND. INDs have been issued to permit patients with serious illnesses, who were not treated satisfactorily with alternative therapy, to be given a promising investigational drug, even though the primary purpose for using the drug in that patient was treatment.

The IND/NDA rewrite proposal (and the proposed DRR act) attempt to formally recognize a situation that currently exists in practice but is not specifically addressed in current regulation. In the drug bill and the IND/NDA rewrite, the term "treatment IND" is defined as a situation where the primary purpose of the use of a drug is not to investigate its effectiveness but to treat, in the context of research on safety, patients having a serious illness that does not respond satisfactorily to currently available alternative therapy. Ordinarily, only drugs sufficiently advanced in the investigational process to be considered in phase III would be the subjects of a treatment IND. Thus, evidence of efficacy would be sufficient that use of the drug by clinicians following a specific protocol would be expected to add safety information useful in the development of labeling for the practitioner, e.g., information on precautions, side effects, etc.

The following administrative revisions relating to procedural issues in IND regulations are being considered: improve structure of initial IND submission so that the scientific data provided would be more clearly linked to the proposed studies in humans; revise IND amendment procedures so that the submissions are more easily reviewable by FDA, providing a more coherent series of additions and modifications to the plan for human studies; and define more carefully the content of required reports on the progress of an IND and, for some

investigational drugs, require periodic conferences between the sponsor and FDA to resolve problems and ensure the efficient use of resources.

Bioresearch Monitoring Program. FDA's Bioresearch Monitoring Program is intended to ensure that drugs and other products regulated by FDA are evaluated on the basis of valid research data (thus protecting the public health) and that human test subjects involved in studies to obtain these data are assured of their rights and safety (thus protecting human test subjects). The ultimate goal of the program, protecting human test subjects and the public, will be met by correcting unreliable research practices associated with the investigation of products regulated by FDA.

The impetus for developing a bioresearch monitoring program—the development, implementation, and continuing management of a program to ensure the quality and integrity of bioresearch data submitted to FDA—stems from FDA's own concerns about data submitted in the past, a General Accounting Office (GAO) report on clinical investigations (July 1976), and hearings held by Senator Kennedy in 1967 and 1975.

The program is directed at both preclinical and clinical studies. In preclinical studies, the program's objective is to ensure the quality and validity of safety data derived from studies in animals. FDA published final Good Laboratory Practices regulations in 1978 (*Federal Register*, December 22, 1978).

For clinical studies, FDA promulgated three separate but closely related sets of regulations. These regulations define the: 1) Obligations of Sponsors and Monitors for Clinical Investigations (proposal published on September 27, 1977); 2) Obligations of Clinical Investigators (proposal published on August 8, 1978); and 3) Standards for Institutional Review Boards (IRB) and Informed Consent (final regulations published on January 27, 1981). Each of the regulations involves a separate and distinct aspect of clinical research but covers overlapping and interrelated issues—for example, the application of "disqualification" as a sanction.

Provisions in each of the final regulations will be coordinated with each other and with related HHS regulations. Thus, each final regulation in the monitoring program, published sequentially, will represent current agency policy in a given area at that time.

Institutional Review Boards. Since 1971, FDA regulations have required that before drugs regulated by the agency may be tested on

human subjects in institutions (including hospitals, nursing homes, mental institutions, and prisons), the proposed studies must be approved and then subjected to continuing review by an institutional review board (IRB). The agency adopted a similar regulatory requirement for studies involving intraocular lenses in 1977 and for other investigational devices in 1980. These regulations provide for the inspection of such IRBs by the agency.

On August 8, 1978, and again on August 14, 1979, FDA proposed to adopt general standards for the composition, operation, and responsibility of an IRB that reviews clinical investigations regulated by the agency under the law (U.S. Congress, 1980a, 360), as well as clinical investigations that support applications for research or marketing permits for products regulated by FDA. (On January 27, 1981, FDA published final IRB regulations, effective July 27, 1981 [*Federal Register,* January 27, 1981].)

In 1972, the FDA Bureau of Drugs initiated a survey of IRB practices and procedures to determine what additional measures were needed to ensure the protection of human subjects in clinical trials. The survey revealed unsatisfactory and/or violative performance in the following areas: patient consent; board structure; board review of projects; and the accuracy and availability of records. FDA presented to Congress the survey results, together with the findings and recommendations of a GAO study critical of clinical drug testing, which charged FDA to develop and implement an intensified program of monitoring clinical investigations, including IRBs. The program was to include uniform standards for IRBs as well as an inspection program to ensure that the standards were being met.

In order to further this objective, the agency was required to publish agency-wide regulations that would set forth the responsibilities of IRBs. The IRB regulations include the following key features and require: institutional assurance of IRB compliance with the regulations; appropriately constituted IRBs; establishment of written procedures for the operation of IRBs; continuing review of clinical research by IRBs; inspection and copying of records; review and approval of informed consent documents and procedures; provisions for suspension for serious noncompliance with the regulations; and retention of records and reports.

Informed Consent. Informed consent is an evolving concept reflecting

ethical and moral attitudes of society. Legal mandates and regulatory requirements for informed consent have changed over the years. Requirements for human subject protection are embodied in provisions of the FD&C act and in regulation. The most widely used are those governing research funded by HHS and codified in the *Federal Register* (January 26, 1981). FDA has specific additional requirements that vary to some extent with the nature of the products being investigated.

The final regulation pertaining to informed consent, published on January 27, 1981 (46 FR 8942), is FDA's mechanism to update and verify current informed consent requirements. This regulation makes a single set of informed consent requirements apply to all investigators involved in studies that either require prior FDA review or would be submitted later to FDA in support of an application.

Agency policy regarding informed consent for use of investigational new drugs on humans was adopted by regulation in 1967 following a reconsideration of the earlier regulations in light of both the Declaration of Helsinki, adopted by the World Health Organization in 1961, and the "Ethical Guidelines for Clinical Investigation," adopted by the House of Delegates of the American Medical Association (AMA) in 1966. The Declaration of Helsinki is set forth in full in the *Code of Federal Regulations* (Code 312.20). The 1967 regulation made two significant changes to the earlier regulation—it allowed oral informal consent in certain cases, and it clarified the information that must be given to the subject before requesting consent.

The 1976 medical device amendments to the FD&C act contain informed consent provisions for medical device investigations that differ from those required for drugs, as defined in current IND regulations. Specifically, exemptions to the informed consent requirements are more tightly drawn than those for drugs under the current regulations.

The current regulations governing informed consent (*Federal Register,* January 27, 1981) make the informed consent provisions of the medical device amendments of 1976—to the extent that they differ from the language of the 1962 drug amendments—applicable to informed consent in investigational drug research. As stated in the preamble to the final informed consent regulation, the policy underlying this approach is that, in light of the nature and concept of informed consent and its basic relation to ethical values rooted in our

society, the particular language of the 1962 drug amendments should not be interpreted literally or strictly as preventing progress in the evolution of informed consent requirements.

The standard of practice regarding informed consent promulgated by Congress in the drug amendments of 1962 was the standard that prevailed at that time. It is not the standard of practice today. FDA is concerned that research subjects be adequately protected from abuses of the kind that have taken place in the past and is convinced that a way to do this is to ensure that they have the opportunity to be adequately informed before they consent to participate.

Congress expressly recognized at the time the medical device amendments of 1976 were passed that, in view of changing social policy and advancing biomedical technology, the informed consent provisions of the medical device amendments should be implemented through regulations based upon the recommendations to be made by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Indeed, the very purpose for which Congress established the National Commission was to ensure a thorough review of the basic ethical principles underlying the conduct of biomedical and behavioral research (*Federal Register,* August 14, 1979).

The FDA regulations published on January 27, 1981, establish general requirements for obtaining informed consent from human subjects and emphasize the need to ensure that the consent be obtained only in a setting where the subject can fully comprehend the information presented, minimizing the possibility of undue influence or coercion and excluding the use of any exculpatory language. Also, they require that information must be given in the primary language of the subject or of his legal representative. They detail situations where informed consent need not be obtained, and they enumerate the specific elements required in informed consent—eight basic items that, as a minimum, must be included in the presentation to the subject. This list of elements was drawn in part from the September 1978 report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, current HHS regulations, existing FDA regulations on new drugs and devices, and the legislative history of the medical device amendments of the FD&C act. Six additional elements of informed consent for an institutional review board to consider in specific cases were included.

As one of its basic elements of consent, the regulation requires that a subject be apprised in advance of the situations in which his or her medical records might be disclosed, situations in which FDA would request access to medical records, and how FDA would safeguard such information. The latter is a controversial issue among clinical investigators; the extent to which it may be of concern to human subjects does not appear significant. Finally, the regulation details the requirements for documenting informed consent, when a witness is necessary, and how oral informed consent should be documented.

Clinical Investigators. FDA's experience shows evidence of noncompliance or inadequate performance by a relatively small number of clinical investigators, as documented by surveys and summarized in congressional testimony over the past decade. The 1972 survey referred to above cited varying degrees of deficiencies that were noted in one or more of the following areas: obtaining and documenting informed consent properly; maintaining records of the disposition of the investigational drug; adhering to the research protocol; maintaining accurate case records on subjects; making all records available to FDA investigators; and understanding the role of the investigator in the research program. Most of those deficiencies constituted violations (in the context of the studies) that did not present any significant hazard to the subject or compromise the integrity of the studies. On the other hand, there was serious concern about certain deficiencies.

On October 11, 1979, the Senate Subcommittee on Health and Scientific Research, Committee on Labor and Human Resources, as part of a series of hearings on the progress of the FDA's Bioresearch Monitoring Program, held a hearing on preclinical and clinical testing under the auspices of the pharmaceutical industry. At that hearing, FDA testified on thirty-one investigators who had committed abuses such as: altered or falsified laboratory work; significant, unreported protocol violations; inadequate proof that the study was actually conducted; falsified patient consent forms and misrepresentation of how consent was obtained; false or misleading evidence of Institutional Review Board approval; falsified patient study records; failure to report concomitant treatments that could invalidate the study; misrepresensentation of medical histories; substantial delay in or refusal of access to records; and flagrant disregard of FDA rules, including testing drugs in human subjects in spite of specific directions not to do so.

Although these deficiencies and abuses are considered unacceptable behavior for clinical investigators, FDA does not believe that these findings indicate that human subjects are routinely being exposed to unnecessary or avoidable risks in the course of research, or that decisions to approve marketing of FDA-regulated products are being predicated on data that are inaccurate or unreliable, or accepted without analysis or means of verification.

Nevertheless, FDA's experience shows that significant deficiencies still exist in the testing of investigational drugs. These deficiencies apply not only to physicians who conduct investigations in their private offices, but also to those doing research in academic institutions with the highest reputations and under government sponsorship. Thus, there is a need to communicate more broadly FDA's policies regarding the conduct of clinical investigators. The proposed regulations, when made final, should accomplish this.

In the proposed regulations, Obligations of Clinical Investigators, FDA announced that the first step toward achieving the compliance of clinical investigators is to restate the agency's policies with precision and to reaffirm the goals being sought. The proposed regulations would clarify existing regulations for clinical investigations on new drug products and extend these regulations to include investigators of other FDA-regulated products. They are largely based upon accepted ethical precepts of medicine and research and accepted standards of good science, and define what FDA expects in the conduct of clinical trials.

Included among the general obligations and commitments of clinical investigators are the following: allow inspection by FDA investigators of facilities and records related to clinical studies; obtain approval by an institutional review board before a clinical investigation is initiated or changed; record the receipt and disposition of test articles in a specific manner; develop and conduct a clinical investigation under a written protocol; obtain appropriate informed consent of human subjects; and maintain records and reports in a specific manner.

FDA's philosophy is that the conduct of clinical investigations is a privilege reserved for those who are able, willing, and successful in conforming to the expected standards of conduct. Disqualification of an investigator is one enforcement option available to FDA if an investigator cannot and does not perform within the expected standards.

Disqualification of a clinical investigator protects the public by

precluding FDA's reliance on unreliable and invalid studies, and it protects patients from being the subjects of poorly managed research. First, it precludes a disqualified investigator from access to any test article until the investigator can demonstrate his or her ability and willingness to conform to expected standards. Second, disqualification provides a mechanism for FDA to refuse to accept data prepared by the investigator in support of an application for a research or marketing permit. Disqualification provides the clinical investigator alleged to have violated the regulations an opportunity for a hearing before the agency.

Concerns have been expressed that the agency would disqualify investigators on the basis of insignificant deficiencies. FDA has neither the inclination, the time, nor the resources to do this. FDA's policy is that disqualification will not be used in trivial situations, but only when the violations materially affect or compromise the integrity of a study or the rights or safety of human subjects.

Disqualification is principally a remedial action to prevent future violations and to ensure that the rights and safety of subjects are appropriately protected and that data in support of applications are produced under circumstances that increase the likelihood of their scientific validity. Therefore, the proposed regulations and current FDA policy provide that disqualification should continue indefinitely unless the agency finds that the investigator can and will fulfill the requirements.

The proposed regulations establish a formal procedure whereby a disqualified investigator who wishes to be reinstated must state in writing why he or she should be reinstated and provide a detailed description of the corrective actions the investigator has taken or intends to take to ensure that the acts or omissions that led to disqualification will not recur.

Obligations of Sponsor/Monitor. As for the conduct of sponsors and monitors, the survey referred to above revealed unsatisfactory and/or violative performance in the following areas: patient consent, protocol adherence, study role, and record accuracy and availability. The proposed sponsor/monitor regulations include the following key features and would require: assurance of IRB approval where applicable; an appropriately trained and qualified individual to monitor clinical investigations; establishment of written procedures for the monitoring of a clinical investigation; that monitors maintain records of required

preinvestigation and provide visits to investigators; adequacy of facilities to be ascertained; procedures to ensure test article accountability and disposition of unused test articles; periodic evaluation of safety and effectiveness data; and retention of records and reports. Many of these practices have already been adopted by sponsors on a voluntary basis, pending publication of the final regulations.

Policy Issues: Challenges and Prospects

Thus far, we have reviewed some of FDA's major pending and existing initiatives and programs. We have also discussed the existing legislative basis for drug regulation and some of the major characteristics of proposed legislative reform. Embodied in FDA's major initiatives and programs and in existing legislation and proposed reform are many difficult policy issues that present FDA with a series of challenges. Some of these policy issues, the challenges they present, and the prospect of meeting them are discussed below.

Treatment IND: The Interface between Research and Treatment

FDA needs to clarify the border between research and treatment involving drugs in the last phase of development, where such drugs are still legally investigational but, from a medical perspective, may be appropriate therapy or even perhaps the treatment of choice.

As mentioned earlier, the IND/NDA rewrite proposal and the proposed Drug Regulation Reform Act attempt to recognize formally a situation that currently exists in practice but is not specified in current regulation. In the administration's drug bill and the IND/NDA rewrite, treatment IND is defined as a situation where the primary purpose of drug use is not the investigation of its effectiveness, but its use to treat patients with serious illness not treated satisfactorily with currently available alternative therapy.

Such a category would not replace the type of studies performed at present in phases II and III but would be an IND category of drugs generally sufficiently advanced in the investigational process to be considered in phase III. Thus, evidence of effectiveness would be

sufficient that use by physicians following a specific protocol would be appropriate in situations where serious disease was present and satisfactory alternative therapy was not available. The research thrust of such IND use would be toward additional safety information, generally of a kind that would be included in labeling information for the practitioner at the time of marketing, e.g., information on precautions, side effects, etc., in the package insert.

There are several reasons why recognition of this situation is important and why it is also controversial. Although this has been FDA's practice for some years (the so-called compassionate IND or emergency IND), there is confusion as to when a drug is ready for such handling by the sponsor of the IND, the FDA, and the clinician. Thus, some drugs that might benefit the patient before marketing approval by FDA (NDA approval) could be made more readily available to patients through such an approach. It is difficult to inform the medical community of such drug availability unless recognition of this status exists in some formal sense. This premarket availability as a compassionate IND was recognized in the case of sodium valproate—an anticonvulsive drug—before final approval for marketing, because of widespread publicity.

An example of an attempt to accommodate this situation in our present system and the controversial nature of such an approach is exemplified by the use of THC (tetrahydrocannabinol)—an active component of marijuana under investigation for the relief of nausea and vomiting secondary to cancer chemotherapy. A special distribution system for investigational drugs operated by the National Cancer Institute (NCI) of the National Institutes of Health (NIH)—the drug sponsor at this time—has recently been approved (Department of Health and Human Services, 1980). Entry of an investigational drug into this system requires a decision on the part of FDA, after a positive recommendation by an advisory committee of expert consultants, that the drug meets the criteria for what is essentially a treatment IND.

The example of THC demonstrates the advantage of the formal recognition of the status of a drug as ready for a treatment/investigational phase—since it is estimated that about 50,000 cancer patients might benefit by such use during this last evaluation phase before marketing. Nevertheless, the THC example also highlights some of the controversy. Specifically, since a drug made available under a

treatment IND does not need to meet the legal definition of effectiveness established in law (as described above), there may be disagreement in the medical and research communities as to how much efficacy needs to be established before entering a drug into a treatment IND phase, as well as whether or not the evidence on safety justified wider investigational-therapeutic use at that time. This issue as it relates to THC was summarized in a journal widely read by health care professionals and the public just before a final FDA decision was reached on such classification (Sun, 1980).

Also, because NCI has an agreement with FDA that concerns only drugs used in the treatment of cancer, such an approach could not easily be used for any other types of drugs at this time, or even for a noncancer-related indication for THC.

There are other societal pressures promoting formal recognition of a treatment research status. For example, legislation establishing marijuana "therapeutic research" programs was enacted in twenty-five states as of October 1980. Other state legislative initiatives have attempted to "legalize" drugs that are either unproved (e.g., Laetrile) or for which IND research either never began or ended when such legislation was enacted. Such attempts to bypass the federal requirements for proving safety and effectiveness are aimed at the investigation-treatment borderland, approximating the treatment IND situation. However, the majority of the marijuana therapeutic research bills require that the state body established to carry out the program deal with the relevant federal agencies to gain IND approval, drug supply, and controlled substance registration approvals (Nightingale and Perry, 1979), thus keeping the treatment thrust firmly within the investigational drug framework.

Other societal pressures would also seem to militate for this kind of designation. Specifically, current governmental policies favor reimbursement for medical services and recognize treatment only, rather than research. Government is only beginning to probe this hazy boundary in the drug area to consider reimbursement for some care related to what legally may be research but in practice may represent the treatment of choice from a medical perspective. Again, NCI's distribution system for investigational cancer drugs is serving to focus the issues.

Congress and the public are becoming more aware of a phenomenon that FDA has recognized for a number of years—namely, the public

health significance of "orphan drugs." These are drugs of little commercial interest. Hence, no matter how much safety and effectiveness data are accumulated, they may never be submitted to FDA in the form of an NDA for formal review. Thus, orphan drugs in phase III clinical trials may never be approved for marketing and may only be available for treatment while legally in investigational status. The sponsors for some of these IND or "service" drugs include Public Health Service agencies as well as commercial firms. Regardless, identifying the IND drugs that offer significant therapeutic advances can assist either in finding a commercial sponsor or in making the terms of marketing such that any potential commercial interest will be increased. A recent FDA publication summarizes a report on this phenomenon and recommendations of a joint government-industry task force (Department of Health, Education, and Welfare, 1979).

Effectiveness: Proposed Federal Legislation and Recent State Actions

As discussed in the second section above, the New Drug amendments of 1962 require that drug manufacturers prove their products effective as well as safe before marketing. Thus, FDA will refuse to approve a new drug application if there is a lack of substantial evidence that the drug will have the effect it purports to have. Under the current law, the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations. The agency, in the NDA section of the *Code of Federal Regulations* (Code 314.111), describes what it considers to be an adequate and well-controlled study within the meaning of the term substantial evidence. As also discussed above in the IND/NDA rewrite section, the agency is reviewing these regulations with an eye to making them more explicit, clearer, and more easily understood by sponsors of new drugs. Although the law requires a showing by a drug sponsor that its product is both safe and effective, the belief in the importance of this requirement is not universally shared, and there is some public dissatisfaction with this basis for drug approval. Such dissatisfaction is best symbolized by the passage of state laws purporting to legalize Laetrile (Nightingale and Arnold, 1978). The public posture—at least that enunciated at state legislative hearings and incorporated into many bills—is that, if the substance is "harmless" or nontoxic *and* if an individual has a life-threatening

disease or is terminally ill, the patient has a right to receive medication as long as it is relatively safe. Although this may mostly represent a testimonial to the vigor and salesmanship of the Laetrile proponents, there are other public expressions of dissatisfaction with the effectiveness requirement.

A bill was introduced in Congress in 1978 and again in 1979 to repeal the effectiveness amendment entirely. Although there have been a large number of co-sponsors each time, hearings have never been held on the bills. On the other hand, new drug legislation introduced both by the administration and by Senator Kennedy and passed by the Senate contained provisions for "breakthrough drugs"—those drugs that hold great therapeutic promise. The standard established for effectiveness is "significant" rather than "substantial" evidence. Approval would be conditioned on the performance of further studies to attain the current statutory standard. Also, some studies to characterize safety could be delayed to a postmarketing phase—one that would, in actuality, be a limited distribution system. An area where FDA has stated that less than the usual requirement for studies to prove effectiveness may be acceptable is the orphan drug situation.

It should be noted that the major direction of legislative thinking has been toward preserving effectiveness as a requirement. Perhaps the most vocal force in all of this are the consumer groups who are in total agreement on the importance of maintaining the current effectiveness provisions without change. Industry and clinical researchers, however, have also supported the effectiveness requirement.

Expediting New Drug Approval versus "Drug Lag"

The term drug lag—a relative delay in the introduction of new drugs, specifically new chemical entities, in the United States—was coined by those critical of FDA's pace in approving new drugs, to label what they perceive to be a serious shortcoming of the regulatory process.

Donald Kennedy (1978), then FDA commissioner, pointed out that superficially it is easy to make the case that a drug lag exists in this country: new drug approvals have declined since the passage of the 1962 drug amendments; the time taken to approve a new drug has increased, and so has the cost of drug development. Further, he acknowledged that drugs available elsewhere are not available in the

United States, and drugs are often approved elsewhere before they are approved in this country.

Kennedy, however, regarded the term drug lag as too loose, obscuring important questions about the quality as distinct from the mere quantity of drug products available in various countries. Citing data for 1976, Kennedy suggested that five other drug-developing countries (England, France, Germany, Italy, and Japan) had experienced what could properly be characterized as a drug lag. Fifteen new drugs were introduced in the United States in 1976, seven of which were previously available in other countries. But by the same token, of the thirty-nine new drugs introduced in Germany, twenty-two were previously available elsewhere, and of the fourteen drugs introduced in Japan, twelve had been made available earlier in other countries.

Kennedy also noted that some of the drugs introduced in the United States in 1976 were available only in this country. He suggested on the basis of this data that a drug lag does exist, but it is experienced by other drug-developing countries as well as the United States, and that the argument that there is something peculiar to our regulatory process that deprives physicians and patients of beneficial new therapies does not stand up under analysis.

How much of the decline in the rate of introduction of new drugs is attributable not to regulation but to exhaustion of certain basic knowledge on which earlier breakthroughs were based? The answer is unclear. One cause for the decrease in the rate of new drug approvals is the increased knowledge of how to test new drugs—new information and more sophisticated techniques relative to pharmacokinetics, analytical toxicology, and requirements to test for carcinogenic, mutagenic, and teratogenic effects (Kennedy, 1978). Other factors include decisions by multinational pharmaceutical companies to introduce a drug abroad because it is convenient to do so even if the drug were developed in the United States. Conversely, the clinical research on a new drug might be conducted outside the United States because of tax advantages, tort liability, patent protection, or the prevailing monetary exchange rate (Kennedy, 1978).

FDA admitted that certain administrative practices—now changed or in the process of changing—did, in certain instances, slow the passage of drugs through the new drug clearance system. Suggestions for improvement in the system were identified by the Dorsen Panel and were discussed elsewhere. The most relevant to the drug lag issue

are those that recommended improving the standards and procedures for premarket approval of new drugs and increasing FDA's authority in the postmarketing period (Dorsen, 1977). The former area included recommendations to amend, by making more precise, the statutory standard dealing with safety and effectiveness to reflect the fact that approvability of a drug entails weighing its risk against its overall benefits; allowing accelerated approval of drugs in certain exceptional cases, such as when a drug represents a major therapeutic breakthrough; completion and release of clinical guidelines for drug testing and pharmacology and preclinical guidelines; and prompt access to FDA reviewer recommendations that might be helpful to drug sponsors.

In the postmarketing period, the review panel recommended an amendment to the FD&C Act to allow FDA to limit the distribution of drugs with unusual benefit and high toxicity to certain settings or specially trained practitioners. Also, the panel recommended that FDA should be authorized to require sponsors to conduct additional research either as a condition of approval or after a drug has been marketed.

Finally, a drug can now be withdrawn quickly from the market only when an "imminent hazard" exists—interpreted to mean an immediate danger to public health. The review panel recommended allowing removal when "substantial risk" of serious harm exists. It was agreed that the above, coupled with further research on how best to monitor for adverse reactions to marketed drugs, would help speed the approval process because more timely and precise knowledge about drug safety would allow FDA to act more swiftly to halt or limit distribution after marketing had begun.

It should be noted that Secretary of Health and Human Services Richard S. Schweiker and Commissioner Arthur Hull Hayes, Jr., of the Food and Drug Administration have placed major emphasis on efforts to speed up the new drug approval process.

International Cooperation

An important, long-term objective relates to establishing meaningful worldwide cooperation among government authorities responsible for granting marketing approval for drugs. An important first step in this process was the first International Conference of Drug Registration

Authorities, cosponsored in October 1980 by the World Health Organization (WHO) and FDA. Great strides were made in opening the lines of communication and cooperation among nations, including initial steps to explore how certain international aspects of the new drug approval process may be harmonized. The potential gains of international cooperation include sharing accurate and timely information on safety concerns about specific marketed drugs so that each nation in which the drug is marketed or under consideration for marketing can review its position vis-à-vis the drug's benefits and risks and determine whether changes in its status are in order. The conference participants also agreed to share information upon which original approval actions were based. It is hoped that the exchange of such information will lead to a more speedy introduction of new drugs worldwide and more appropriate decisions on marketed drugs.

This conference was the first opportunity for drug registration authorities from around the world to meet and get to know one another, an important outcome of the meeting. The presentations, workshops, and discussions set the stage for future informal as well as formal sharing of information and guidelines among nations. This exchange cannot fail to have a salutory effect. The challenge is to each country, however, to maintain contacts with counterparts in foreign governments—notwithstanding turnover in personnel and changes affecting the bureaucratic locus or structure of each country's drug registration authority.

Another important challenge grows out of the discussions on harmonization. Two areas were selected in which to explore harmonization in the new drug approval process. The first is the development of uniform format and content requirements for drug approval applications. In their discussions in this area, the delegates recognized the important role of national legislation governing the new drug approval process and the concerns of the pharmaceutical industry in harmonizing drug approval documents required by various countries. WHO was to take the lead in meeting with the pharmaceutical industry to solicit advice on this subject. The second area relates to harmonization of technical aspects of guidelines, including guidelines for clinical trials, preclinical studies, etc. Here, too, the need for industry cooperation was well recognized by the conference participants.

All of the recommendations were made in an atmosphere of cooperation and enthusiasm generated by the session. Clearly, FDA,

WHO, and the other participating countries must aggressively pursue the conference recommendations. The consensus of the group was that it would be ideal to meet every two years or more often. The types of activities under consideration, however, should not be left to be deliberated only at a major international conference, but will be the subject of continuing informal discussions. The Second International Conference of Drug Registration Authorities will be held in Rome in the fall of 1982.

Meanwhile, FDA intends to take significant independent actions to facilitate drug development in the international sphere. Some of these are already in process or under review. FDA plans to clarify its acceptance and use of data that are developed in other countries and submitted to the agency as part of a new drug approval application. The IND/NDA concept paper discussed earlier addressed this issue, and the proposed regulations will be one vehicle for needed clarification. Of particular importance, however, will be the provisions of each of the individual final Bioresearch Monitoring Program regulations (also discussed earlier) as they relate to the acceptance of foreign studies in support of applications submitted to FDA. For example, how FDA deals with the requirements for the conduct of IRBs, informed consent, and the obligations of clinical investigators, and sponsors and monitors in foreign studies in its final regulations will have great significance for national and international drug development. The FDA is factoring these considerations into its final regulations.

Concurrently, FDA is entering into Memoranda of Understanding with various countries relative to the inspection of laboratories under the Good Laboratory Practices regulations. The extent to which this is desirable and practicable in other Bioresearch Monitoring Program areas depends on the specifics of the regulations when they are made final.

Conclusion

The American system of drug regulation has evolved over the past seventy-five years in response to advances in the sciences underlying pharmaceutical therapeutics and changes in society's expectations regarding drug development and drug therapy. The major issues facing

drug regulation concern not only ensuring the safety and effectiveness of drugs approved for marketing, but also the quality of the research on which approval decisions are based, protection of the rights of human subjects on whom investigational drugs are tested, and the extent to which the review process can be accelerated without jeopardizing the public health. These issues are under intense scrutiny within and outside government in the United States and abroad. It appears likely that the drug review process will undergo significant modification in the years ahead, as it has at several points in its history going back to the early years of this century.

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