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The Drug Approval Process;

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A drug's sponsor must provide: 1) adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested; and 2) substantial evidence that the drug will have the effect it purports or is represented to have. "Substantial evidence" means "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 fairly and reason-

ably be concluded by such experts that the drug will have the effect it purports or is represented to have" (21 U. S. C., sec. 355(d)). (See app. A for selected sections of the act.)

This statutory language has led the Food and Drug Administration (FDA) in practice to establish a premarketing phase of drug testing that consists of two parts: 1) the investigational new drug (IND) application process, and 2) the filing of a new drug application (NDA).

NOTICE OF CLAIMED INVESTIGATION FOR A NEW DRUG

IND Application Process

A new drug is defined as any drug: 1) that is not generally recognized by experts to be safe and effective for the use described in the drug's labeling (except for certain so-called "grandfather drugs," i.e., those approved prior to the 1962 amendments); or 2) that has been shown to be safe and effective in clinical investigations, but has not been used to any material extent or for a material time.

A drug is considered to be new for any of the following reasons: 1) it is composed in whole or in part of a new substance (this includes active components and inert ones, such as a coating or carrier); 2) it is a new combination of approved drugs; 3) it is an approved combination in a new ratio; 4) it is an approved drug with a proposed new use (i. e., a use for which the drug has not been approved); or 5) it is an approved drug with a proposed new dose *or* new method or duration of administration (21 CFR 310.3(g)).

A sponsor is the entity responsible for the entire investigation of a new drug. The sponsor can be an individual, a partnership, a corporation, or another agency of the Government (e. g., the National Cancer Institute). In testing a new drug, a

sponsor may use a number of different investigators.

A sponsor wishing to investigate a new drug by means of clinical tests in humans must first carry out various studies in animals (see table 1). Such studies examine acute and chronic drug toxicity at different dose levels, by different routes of administration, and in different species. Biochemical data are also obtained on the drug's absorption, distribution, metabolism, and excretion. The data from chronic animal studies, which can take over 2 years to collect and analyze, are not ordinarily required for permission to proceed to human trials. Long-term animal tests must also be undertaken at the same time that the drug is being tested in humans, particularly for drugs intended for use over long periods of time, as for chronic diseases and oral contraception. The purpose of long-term animal tests is to investigate the drug's toxicity (e.g., carcinogenicity) when taken chronically, and its effects on fertility, reproduction, and fetal development (e.g., teratogenicity).

The point at which FDA becomes involved in the development process for a new drug is when a sponsor desires to investigate the drug's safety and effectiveness via clinical tests in humans, Be-

Table 1.—Guidelines for Duration of Animal Toxicity Studies for Oral and Parenteral Drugs

Expected duration of continuous administration to humans	Phase of clinical investigation	Duration of subacute or chronic toxicity studies in animals
Several days	I, II, III, NDA ^a	Two species; 2 weeks
Up to 2 weeks	I	Two species; 2 weeks
	II	Two species; 2 months
	III, NDA ^a	Two species; up to 3 months
Up to 3 months	I, II	Two species; 4 weeks
	III	Two species; 3 months
	NDA ^a	Two species; up to 6 months ^b
6 months to unlimited	I, II	Two species; 3 months
	III	Two species; 6 months or longer
	NDA ^a	Two species; 12 months ^b (nonrodent) 18 months ^b (rodent)

^aNew drug application^bAlthough there has been no formal updating of these guidelines, they have been expanded to include 2-year animal toxicity and carcinogenicity studies for those drugs that would be administered chronically or intermittently in a large population (e.g., contraceptives). These studies are presently being required on a drug-by-drug basis as investigational new drugs are reviewed.

SOURCE U.S. Food and Drug Administration

fore proceeding, the sponsor must file an IND application with the Office of Drugs in FDA's National Center for Drugs and Biologics. The 1962 amendments to the Food, Drug, and Cosmetic Act, by empowering the Secretary of Health and Human Services to write specific requirements, effectively require that all results from testing a new drug in humans be submitted by the sponsor of the drug and approved by FDA under an IND. In filing the IND application, the sponsor agrees to refrain from beginning studies for 30 days, but may begin them after that time unless FDA asks the sponsor to continue to avoid or to restrict use of the drug in humans. The 30-day delay can be waived upon a showing of good reason.

The IND application describes the qualifications of the investigators and the planned trials, and includes a chemical description of the drug and available data on its pharmacology and toxicology as collected in animal studies and in prior human studies, if any (e.g., those conducted in foreign countries). If the necessary animal tests have been carried out and give evidence for the safety of the proposed human use, if the drug is adequately characterized so that the tests will be meaningful, and if the proposed human studies appear reasonably safe, the IND application is usually approved. The sponsor may then proceed with clinical testing if FDA does not raise objections within 30 days.

Once the IND application is approved, additional protocols and investigations can be added. FDA sets no time limit on the IND process as long as annual reports in the form of summaries are submitted and serious adverse reactions are promptly reported. All data on drug effectiveness, including that from clinical studies in patients, as well as chemical and animal data, are considered to be the sponsor's property and subject to protection as trade secrets. If, at any time during the tests on human subjects, the continuance of those tests is determined to endanger public health, they can be stopped immediately.

The clinical investigations of a new drug—i.e., studies in humans—are divided into three phases that in actual practice are not so distinctly separated (see table 2) (24).

Phase I: Clinical Pharmacology is the initial use of the drug on humans. The purpose of this phase is to determine levels of tolerance (toxicity), to begin to ascertain safe dose ranges, and, in some cases, to study drug efficacy in selected patients. The total number of healthy volunteer subjects and patients administered the drug ranges from about 20 to 80. At this stage, many drugs are screened out because their safety is found to be seriously questionable or because they are found to be inactive in humans. If the drug appears to be well tolerated, it may go on to the next stage of testing.

Table 2.—Studies Required in FDA's Premarketing Drug Approval Process**Phase 1:**

- Studies in normal volunteers or relatively healthy patients to determine safety and pharmacologic effects.
- Small studies in patients to determine clinical effectiveness.
- Total number of subjects—up to 80 administered the investigational drug.

Phase II:

- Controlled clinical trials to determine appropriate doses, safety, and effectiveness.
- Total number of patients—about 200 administered the investigational drug.

Phase III:

- Controlled and uncontrolled clinical trials to determine safety and effectiveness and to support labeling claims.
- Total number of patients—about 500 to 3,000 administered the investigational drug.

SOURCE U S Food and Drug Administration

Phase II: Clinical Investigations are the earliest investigations specifically designed to demonstrate effectiveness and relative safety, and to include controlled studies. In this phase, the drug is administered to 100 to 200 patients, under rigid protocols and close monitoring. If the therapeutic value of the drug has been demonstrated, and it appears to have no serious adverse effects, it may then enter the final stage of testing.

Phase III: Clinical Trials are expanded controlled and uncontrolled trials. They are carried out on 500 to 3,000 patients in situations similar to those of actual clinical practice—in clinics, outpatient hospital facilities, and private practice. These studies are performed after a drug's efficacy has been established, at least to some degree, and are intended to gather additional evidence of drug effectiveness, to discover rarer drug effects or effects that develop after longer periods, and to better define the frequency and severity of more common effects as well as the proper use of the drug (e.g., by identifying best dose, dose interval, and the drug's interactions with other drugs). Adequate and well-controlled trials that give evidence of a drug's effectiveness, accompanied by complete case records for each patient, are sometimes

termed pivotal studies. FDA usually requires at least two independent well-controlled studies to approve an NDA, the following stage of the drug approval process, though more than one drug indication can be evaluated in a single study. (These requirements are currently under review; see ch. 3.)

Compassionate or Treatment IND

FDA has recognized that under special circumstances, when a patient has exhausted all other therapies for a life-threatening disease, a drug that might be of value but is still unapproved should be made available. Investigational drugs can be made available under a "compassionate" or "treatment" IND. The drugs made available are generally in phase III of clinical testing.

Physicians can obtain an investigational drug if they have a patient with a disease that is life-threatening or significantly impairs the quality of life, and the patient is allergic or resistant to existing methods of treatment. Under such circumstances, FDA usually recommends that the physician contact the medical director of the company investigating the drug to inquire whether the company will accept the physician as an investigator under its IND application for that particular patient. The company may also supply the drug to the physician, who files his or her own IND application.

Sometimes these treatment uses can become quite extensive, especially when available therapy is unsatisfactory, for example, in the treatment of serious cardiac arrhythmia and angina pectoris. According to Robert Temple, recently appointed director of the Office of Drugs' New Drug Evaluation Division, promising new antiarrhythmics and antianginal drugs have been given to thousands of patients under these circumstances. But the compassionate IND procedure may be inadequate for providing a needed drug that is still in the process of being approved when patients are distant from a medical center or when physicians are not familiar with FDA procedures.

THE NEW DRUG APPLICATION PROCESS

After the completion of required testing under the IND, if the sponsor believes that the drug's safety and effectiveness have been proved and that the drug has commercial potential, the sponsor may file an NDA, a request for FDA's permission to market the drug in interstate commerce. This application includes everything the sponsor considers necessary for meeting the statutory requirements: 1) full reports of animal and clinical studies carried out to determine whether the drug is safe and effective; 2) a statement of the drug's composition; 3) a description of the methods, facilities, and controls used in the drug's manufacturing, processing, and packaging; 4) samples of the drug and its components as may be required; and 5) a copy of the proposed labeling. The labeling describes what is known about the drug: the approved uses, dosages, the indications for which its effectiveness is approved, and its known adverse side effects. The final wording of the labeling is negotiated between FDA and the sponsor, and must be formally approved as part of the NDA.

All INDs are classified by chemical type and therapeutic potential so that those drugs considered by FDA to be of particular therapeutic importance can receive priority review (see table 3). The highest classification is for a drug that is both a new molecular entity (type 1) and that might represent an important therapeutic gain (type A)—a type 1A drug. The next highest classification is given to a new molecular entity that represents a modest therapeutic gain (a type IB drug). But skepticism has been expressed by some industry representatives as to whether a correct determina-

tion of the potential benefits of a drug can be made at the time of NDA submission,

After the NDA is filed, a team of FDA reviewers analyzes the sponsor's summaries of the data or, when needed, the actual data. The review team includes a physician, who reviews the clinical test results; a pharmacologist, who reviews the animal test results; and a chemist, who reviews the chemical data and manufacturing controls and processes; supported by a biopharmaceutical specialist, a biometrician, and, when applicable, a microbiologist. The main objective of the process is to ensure that the data from the clinical experiments support the claims for the drug's safety and efficacy in the labeling the sponsor submitted.

NDAs may be presented for consideration to advisory committees composed of experts (mostly nongovernmental) in the various subspecialties of medicine, in clinical pharmacology, and in biometrics. The committees recommend whether or not an NDA should be approved to market a drug and, if the drug is approved, what wording should appear in its labeling. They also may recommend whether the sponsor should be requested to carry out additional studies after the drug is marketed. If the committees recommend against approval, they identify deficiencies and may suggest new studies that need to be done by the sponsor to further investigate the drug's safety and efficacy.

FDA invites a sponsor to confer with FDA about important new therapeutic drugs during the drugs' investigational phases. Usually, such conferences are arranged at the end of phase II, when a drug's degree of efficacy and safety has been

Table 3.—FDA's Drug Classification System

Chemical type	Therapeutic type
Type 1 New molecular entity	Type A Important therapeutic gain
Type 2 New salt, ester, or derivative	Type B Modest therapeutic gain
Type 3 New formulation	Type C Little or no therapeutic gain
Type 4 New combination	Type D Decreased safety or efficacy
Type 5 Duplicate of an already marketed drug	compared with other drugs but has some compensating virtue
Type 6 Already marketed product by same firm—primarily used for new indications	

SOURCE U S Food and Drug Administration

largely established. The purpose of the conferences is to discuss whether the studies to date are acceptable, in view of the drug's proposed indications and the claims made for the drug, and whether the additional controlled studies proposed for phase III will be adequate for the NDA's approval.

FDA must approve or disapprove a submitted or resubmitted NDA within 180 days. It may take longer if the sponsor and FDA agree on an additional period of time. An FDA study of the review time for approved NDAs found that in 1976, it was 25.9 months, in 1977, 26.6 months, and in 1978, 33.3 months (12). In the first half of 1979, however, the average time had been reduced to 20 months (30). These approval times include several resubmissions of the NDAs either to correct deficiencies noted in them during FDA review, or because the sponsor obtained a large amount of additional data. Furthermore, the total amount of information required for an NDA has increased markedly since 1938, when the 180-day limit was imposed. In 1938, the required information consisted of data from short-term animal toxicology studies, along with that from a few studies in humans. Today, an NDA must contain the reports of numerous short- and long-term animal studies along with the reports of various clinical trials to demonstrate the drug's safety and effectiveness in humans.

Should FDA decide to refuse approval, the sponsor receives a "nonapprovable" letter explaining why the NDA fails to fulfill statutory requirements. An applicant's approval can be refused for any of the following reasons:

- Drug safety has not been studied by all reasonably applicable tests.
- The drug is not safe for the intended use.
- The drug's manufacturing processes are not adequate to ensure its identity, strength, quality, and purity.
- Substantial evidence of the drug's effectiveness is lacking; i.e., the clinical investigations were not adequate or well controlled or their results do not adequately support the claims made.
- The labeling is false or misleading in any particular.

Ž The application is missing data, e.g., on bioavailability or bioequivalence or on the environmental impact of the manufacturing process.

If the clinical trials establish that a drug is effective for its intended indications, FDA must decide whether the drug's benefits outweigh its risks. FDA does not require a sponsor to prove that a drug is safer than available drugs, nor more effective, nor even as effective as other treatments in order to receive permission to market the drug. In some cases, a drug may be less safe than an alternative therapy. Although most manufacturers normally would not be interested in marketing a drug whose benefit/risk ratio is less than that of a treatment already available, FDA recognizes that there are times when such drugs should be made available.

When presented with an NDA in which the data clearly show a drug to have an inferior benefit/risk ratio, FDA considers the indications for which the drug is offered. Thus, such drugs when intended to treat a life-shortening condition might receive approval, while such drugs when intended for lesser indications (e.g., mild analgesics that are less safe and no more effective than aspirin) would not. Obviously, the decisions that cause the most difficulty are those concerning drugs between these extremes (22).

Abbreviated New Drug Application

FDA has established an abbreviated new drug application (ANDA) for generic versions of drugs first marketed between 1938 and 1962. These drugs require less testing for approval than do original versions of a drug. The amount of information required for approval of such generic drugs varies, depending on the nature of the drug. The ANDA policy does not apply to drugs marketed after 1962. Approval of generic copies of these recent drugs requires a standard NDA, but FDA has been willing to accept published reports demonstrating the safety and efficacy of these drugs. NDAs that rely on published reports are sometimes referred to as "paper" NDAs.

REQUIREMENTS FOLLOWING APPROVAL

Once the NDA has been approved, the sponsor is required to keep records and submit reports about the drug. This information is used to: 1) maintain the procedures and safeguards for manufacturing established during the approval process, 2) ensure that there are limits placed on advertising and promotional claims and that the drug's labeling is appropriate, and 3) provide the basis for FDA's removal of a drug from the market, when such action is appropriate.

The studies carried out before a drug is released have a number of inherent limitations with respect to the amount and kind of information they generate, limitations that include the following:

- The patients in premarketing studies (even in phase III) do not represent all those who would ultimately take the drug. Thus, a drug's effects on special patient populations not specifically studied in premarketing tests may not be known. Such special populations include patients who are taking several medications concurrently, those having diseases in addition to the one treated by the drug, and those who suffer more severely from the disease being treated than the patients in the study groups. Similarly, when phase III studies are conducted on children (e.g., when they are to be a drug's chief recipients), usually only very small groups of patients are studied, and the entire age range of concern (e.g., including newborns) is not studied for ethical and other reasons.
- The total number of people exposed to the drug in premarketing studies is relatively small; therefore, uncommon adverse reactions (i.e., those less frequent than 1/1,000) are unlikely to be detected.
- The duration of exposure to the drug in premarketing studies is relatively brief (12 to 24 months at most); therefore, adverse effects that only appear after long-term use or that require a latent interval after exposure to develop (e.g., cancer) cannot be detected.
- Clinical trials must be conducted according to strict protocols (regarding dosages, duration of treatment, etc.), and they are usually carried out by specialists in large medical

centers where such research can be done. Thus, the effects a drug might have when administered by a regular physician in an office or outpatient clinic, when patient compliance to a treatment regimen is less controlled, cannot be fully assessed.

- In premarketing studies, a drug is often evaluated for only one purpose (e.g., treatment of hypertension), but it may have another use (e.g., treatment of angina pectoris). (In its labeling, the only drug indications that may appear are those that have been explicitly tested and approved).

FDA has several mechanisms to obtain information about drugs once they have been approved for marketing.

FDA may request further studies when questions about a drug remain unanswered by phase III studies but do not warrant delaying the release of what may be a useful new product. These studies are referred to as "phase IV" studies. Although this designation is not defined in FDA regulations, it is discussed in the guidelines (24). The studies' nature depends on the question to be resolved, and their design is negotiated between the drug's manufacturer and FDA through its New Drug Evaluation Division in the Office of Drugs.

Phase IV postmarketing studies can be of several types (24):

- Additional studies to elucidate the incidence of adverse reactions, to explore a specific pharmacologic effect, or to obtain information of a circumscribed nature.
- Large-scale, long-term studies to determine the effect of a drug on morbidity and mortality.
- Additional clinical trials similar to those in phase III, to supplement premarketing data where it has been deemed in the public interest to release a drug for more widespread use prior to acquisition of all data which would ordinarily be obtained before marketing.
- Clinical trials in a patient population not adequately studied in the premarketing phase; e.g., children.

- Clinical trials for an indication for which it is presumed that the drug, once available, will be used.

In general, phase IV studies have been requested when a drug is likely to be widely used, and important safety and efficacy questions about it remain. Phase IV studies may be requested, for example: 1) when there are suspected or known adverse drug reactions (ADRs) associated with the drug, in order to confirm the ADRs and to determine their true incidence; 2) when a drug belongs to a class of drugs known to be associated with a serious ADR, but its incidence may not be high enough to observe in the limited number of patients in phase III studies; 3) when the drug is one that will be used with children, and it was not tested on them in the premarketing studies; 4) if the drug is likely to be used therapeutically in combination with another drug, and there is reason to be concerned about the toxicity of the combination; and 5) if a drug approved for one indication is very likely to be used for several other indications. (Studies may be required for each of the other uses. For example, most beta-adrenergic blocking agents, such as propranolol, are used in the treatment of angina, hypertension, and arrhythmia, but an NDA may be approved when the use of a drug for only one of these indications has been documented. Even though the drug has only one approved use, it will likely be prescribed for the other two uses.)

Phase IV studies may be typical clinical trials similar to those carried out in the premarketing period. They may also use other surveillance methods. (See ch. 4 and its case studies of streptokinase and cimetidine.)

Finally, FDA receives information on marketed drugs through various kinds of monitoring of adverse drug reactions carried out by the Division of Drug Experience in the Office of Drugs:

- the Spontaneous Reaction Reporting Program, in which ADRs are reported to FDA by physicians, pharmacists, hospitals, and manufacturers (the last kind of reporting is mandatory);
- a monthly review of the medical literature on ADRs (reports to medical journals, letters to the editor, etc.);
- intensive surveillance and epidemiological studies of ADRs in selected hospitalized and ambulatory populations;
- several specialized registries that collect and analyze possible ADRs; and
- the World Health Organization (WHO), which sends reports to FDA summarizing the ADRs added to its system in the previous year. FDA reciprocates by providing U.S. data to WHO.

This report focuses on the regulatory uses of such postmarketing surveillance. Past studies of this issue have also focused on the need for systematic evaluations in the postmarketing period regardless of their importance for regulation, for example, in order to build a resource base of scientists, evaluation methods, and data sources for the better understanding and use of drugs once they are marketed. The evolutionary context of postmarketing surveillance is summarized in chapter 3.