Clinical Testing

Synopsis of the New Drug Regulations

The 1962 amendments to the Federal Food, Drug, and Cosmetic Act strengthen the regulatory authority of the Government over clinical testing of new drugs in order to minimize hazards inherent in new drug development and to assure a responsible concern for the well-being of human subjects. Furthermore, the new regulations establish a strong basis for promotion of improved methods and evaluation of standards in investigation of new drugs.

This synopsis outlines the physician's responsibilities, under the Act, to the patients, to the pharmaceutical company, and to the Food and Drug Administration.

Definition of a New Drug

A new drug cannot be distributed interstate for use in man, without approval by the Food and Drug Administration. An exemption is required to permit clinical investigation.

Unless a drug is generally recognized by qualified experts as being safe and effective for the use proposed, it must be regarded as a "new drug." If there is uncertainty, the FDA will furnish its judgment on request.

A drug may be "new" without necessarily being a new substance. For example, if aspirin tablets were labeled or promoted as a seasickness remedy, they would be considered a "new drug." Even an accepted remedy, used for years, if manufactured in a new form, such as a timed-release capsule, is considered to be a new drug requiring evaluation by the FDA. Clinical investigation may be required to show that the active substance is released in a slow and sustained manner, and that the capsule is safe and effective as claimed.

First Steps in the Assessment of a New Drug: "IND"

Before a new drug may be tested on human beings, the "sponsor" (usually a pharmaceutical firm, sometimes an investigator) must supply to the FDA the information specified as a "Notice of Claimed Investigational Exemption for a New Drug" (Form FD 1571), known as an "IND." Copies of these IND forms are contained in the Investigational Drug Regulations, which may be obtained on request.

The IND is usually required to include, among other things, the following information:

a) Complete composition of the drug, its source, and manufacturing information, adequate to show that appropriate standards exist to insure safety.

b) Results of all preclinical investigations, including animal studies. Initially, these should be directed toward defining its *safety*, rather than its efficacy. The data must demonstrate that there will not be unreasonable hazard in initiating studies in human beings. Further animal studies may be conducted concurrently with clinical studies. The Bureau of Medicine will, on request, comment on the adequacy of proposed animal studies. The FDA generally requires as a minimum that acute toxicity be determined in two species of animals, that results of administration of the drug for two to four weeks be observed in at least two species, and that the route of administration be that which will be used in the human trials. Additional animal studies are frequently necessary.

c) A description of the investigations to be undertaken.

d) Information regarding training and experience of the investigators. (See "Qualifications of Investigators" below.) Investigators are responsible to the sponsor and are required to submit, to the *sponsor* (not the FDA), either Form FD 1572 for clinical pharmacology or Form FD 1573 for clinical trial.

e) Copies of all informational material supplied to each investigator. (The type of information is listed in Form FD 1571.)

f) An agreement from the sponsor to notify the FDA and all investigators if any adverse effects arise during either the animal or human tests.

g) Certification that "informed consent" will be obtained from the subjects or patients to whom the drug will be given.

h) Agreement to submit annual progress reports.

Physician-Sponsored IND

When an investigator wishes to act as sponsor for the use of a drug solely as a research tool or for early clinical investigation of a drug of therapeutic or diagnostic potential (clinical pharmacology—phases 1 and 2) a simpler abbreviated form of submission is acceptable. An example would be the study of a drug

that no manufacturer is interested in sponsoring. An outline of such a study should provide the following information:

1. The identity of the compound or compounds, together with the facts that satisfy the investigator that the agent may be justifiably administered to man as intended.
2. The purpose of the use and the general protocol.
3. Appropriate background information, including a brief statement of the investigator's scientific training and experience and the nature of the facilities available to him.

The physician sponsoring this form of IND deals directly with the FDA and is responsible for compliance with the procedures set forth in this synopsis.

Phases of Clinical Investigation

The first two phases are described as clinical pharmacology.

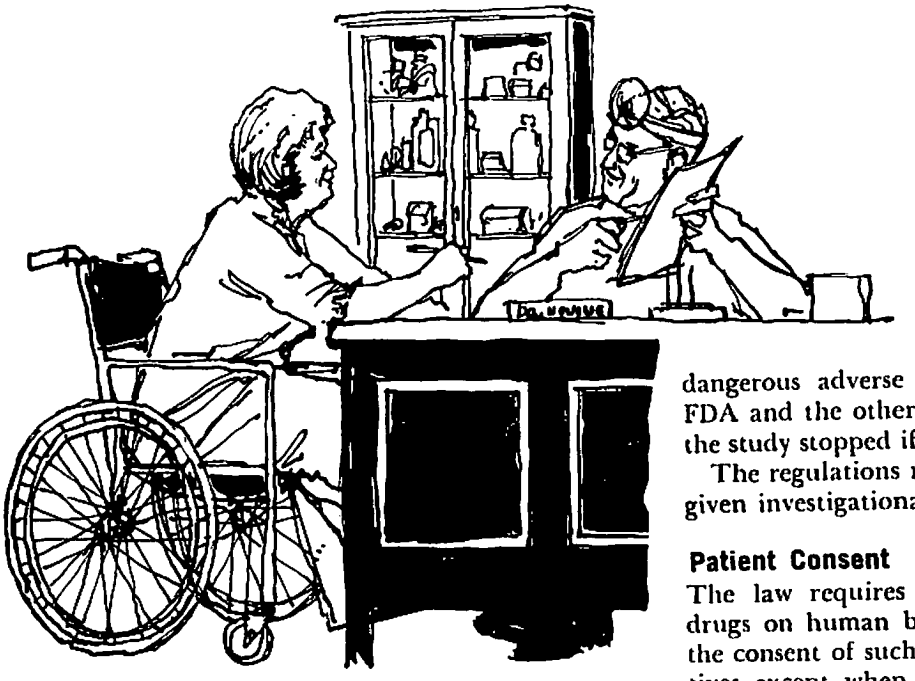
In the *first phase,* the drug may be administered to healthy volunteers, the object being to determine toxicity, metabolism, absorption and elimination, other pharmacological action, preferred route of administration, and safe dosage range. Such studies involve a comparatively small number of subjects and are ordinarily conducted under carefully controlled circumstances by persons with training in clinical pharmacology. The proposed clinical plan may allow considerable flexibility.

When phase 1 demonstrates satisfactory results, the sponsor may proceed to *phase 2:* initial trials in the treatment or prevention of the disease for which the drug is intended, in which the drug is administered to carefully supervised patients to determine safety and effectiveness. Additional pharmacologic studies, performed concurrently in animals, may be necessary to indicate safety for the phase 2 extension of the investigation.

The FDA is always willing to consider reasonable amendments to clinical plans and to discuss with sponsors the value of proposed studies. Of course, a plan of investigation may be revised during its course, but in each such instance the FDA must be notified.

Finally, if the data obtained in phases 1 and 2 provide reasonable assurance of safety and effectiveness or suggest that the drug may have a potential value outweighing its hazards, proposals for *phase 3,* or extensive clinical trials, are in order. Phase 3 may, where practical, involve, in addition to work by experienced investigators, well-controlled studies by other groups including practicing physicians whose training and experience in drug evaluation has been less, and whose facilities may not be so elaborate. The studies should be carefully monitored, no matter how extensive. The regulations are designed to prevent exposure to risk of an unnecessarily large number of patients by requiring assurance of safety based on earlier studies.

Once an IND has been submitted, the investigation may then proceed, unless the FDA presents an objection. If there appears to be an unwarranted hazard in the continuation of the ongoing clinical studies, the sponsor may be requested to modify or discontinue clinical testing until further preclinical work has been done. An important function of FDA reviews is to inform the sponsor regarding further investigation required before extending the clinical testing to another phase.



Qualifications of Investigators

The sponsor of an investigational new drug (usually the manufacturer) will ask the clinical investigator to supply the following information on Form FD 1572 (for the clinical pharmacologist engaged in phase 1 or 2 trials) or Form FD 1573 (for the physician engaged in phase 3 clinical trials):

1. A statement of his education, training and experience which qualify him. ("Curriculum Vitae.")
2. Information regarding the hospital or other medical institution where the investigations will be conducted, special equipment and other facilities.

The training and experience needed will vary, depending upon the kind of drug and the nature of the investigation. In phase 1, the investigator must be able to evaluate human toxicology and pharmacology. In phase 2, the clinicians should be familiar with the conditions to be treated, the drugs used in these conditions and the methods of their evaluation. In phase 3, in addition to experienced clinical investigators, physicians not regarded as specialists in any particular field of medicine may serve as investigators. At this stage, a large number of patients may be treated by different physicians so that a broad background of experience may be secured.

Obligations of Investigators

The investigator must keep careful records of his study and retain them for at least two years after completion. The records must be made available promptly to the drug sponsor and to the FDA when required. Progress reports must be sent to the sponsor (in practice usually the manufacturer) at intervals not exceeding one year.

Emergency reports must be sent to the sponsor when dangerous adverse effects are observed, so that the FDA and the other investigators can be notified, and the study stopped if the hazard warrants.

The regulations regarding consent of human beings given investigational drugs must be observed.

Patient Consent

The law requires that before using investigational drugs on human beings, the physician must "obtain the consent of such human beings or their representatives except when it is not feasible or when in his professional judgment it is contrary to the best interest of such human beings." This means that the consent of persons (or the consent of their representatives) to whom investigational drugs are administered primarily for the accumulation of scientific knowledge must always be obtained; where patients are given a new drug for *treatment*, consent must also be obtained in all but exceptional cases. These exceptions are defined in the law as situations "where it is not feasible to obtain the patient's consent or the consent of his representative or where as a matter of professional judgment exercised in the best interest of a particular patient under the investigator's care it would be contrary to the patient's welfare to obtain his consent."

The consent for use of an investigational new drug in phase 1 and phase 2 must be in writing; in phase 3 it is the responsibility of the investigator, taking into consideration the physical and mental state of the patient, to decide when it is necessary or preferable to obtain consent in other than written form. If written consent is not obtained, the investigator must obtain oral consent except as provided above, and record that fact in the medical record of the person receiving the drug.

Causes for Termination of Investigation

The FDA may direct the sponsor to terminate an investigation at any stage under stated conditions. These include:

Evidence of significant hazard.
Convincing evidence that the drug is ineffective.
Submission of false data.
Omission of material information.
Unsatisfactory manufacturing practices.

Failure to conduct the investigation in accordance with the plan submitted by the sponsor and approved by the FDA.

Commercialization of the drug. The IND regulations are not intended to provide a way of marketing a drug for profit without an approved NDA.

Failure to submit progress reports at intervals not exceeding one year.

Failure to report serious or potentially serious adverse reactions.

Failure to meet requirements for patient consent.

The Commissioner may notify the sponsor of any of the above conditions and invite immediate correction. A conference may be arranged. If the corrections are not effected immediately, the Commissioner may require the sponsor to terminate the investigation and recall unused supplies of the drug. The drug in question may not be reintroduced into clinical testing in man until additional data have been submitted to the FDA and the Commissioner has approved the proposed resumption of the study.

The Investigator and "Promotion"

The regulations forbid manufacturers or any persons acting for or on their behalf to disseminate any promotional material concerning a new drug prior to completion of the investigation. This is not intended to restrict the full exchange of scientific findings in scientific or lay communications media; its sole intent is to restrict promotional claims by the sponsor until the safety and effectiveness of the investigational drug have been established. Violation of the regulations by an investigator may result in FDA action to deny him further supplies of the drug; the manufacturer may also jeopardize *his* right to sponsor the investigation.

Special Preclearance before Human Trials

While the sponsor may ordinarily inaugurate a study as soon as the IND is submitted to the FDA, there are certain exceptions calling for preclearance. *Before* starting an investigation in any of the following categories, FDA approval is required.

a) investigations of hallucinogenic drugs, such as LSD,

b) investigations of drugs so toxic that their use may be justified only under special conditions, such as DMSO,

c) reinstitution of drug investigations which had been terminated by the Commissioner.

Use of Drugs for Laboratory Procedures

New drugs used only for studies in vitro or in laboratory animals are exempted from the new-drug provisions of the Act provided they are labeled "Caution —Contains a new drug for investigational use only in laboratory research animals, or for tests in vitro. Not for use in humans."

The exemption does not apply, however, for a new drug used in vitro when this use will influence the diagnosis or treatment of disease in a human patient—for example, discs to determine the sensitivity to anti-

biotics of bacteria in culture, or a stick or strip of paper incorporating a reagent to test for sugar in the urine. Apparent ineffectiveness of an antibiotic sensitivity disc or a false negative test for glycosuria might well lead to an incorrect diagnosis and deprive the patient of appropriate treatment.

Before such a preparation can be marketed there must be certification (in the case of antibiotics) or approval of a New Drug Application (in the case of other drugs). For that reason, it is necessary to submit adequate proof of the effectiveness of these preparations before they can be marketed.

New Drug Application: "NDA"

After the human pharmacological and clinical studies previously described have been made, and the manufacturer is convinced that the new drug is safe and effective, he submits a New Drug Application ("NDA"), on Form FD-356 with supporting data and proposed labeling to show that "it could fairly and responsibly be concluded by qualified experts that the drug is safe and will have the effect it purports or is represented to have under conditions of use prescribed, recommended or suggested in the proposed labeling."

If the investigational new drug studies were well conducted, step by step, through each phase of investigation, the FDA would have in its hands at the end of phase 3 the complete information needed for an NDA which could be promptly approved. In practice, however, this has frequently not been true.

The FDA is required to act on the Application within 180 days. FDA action takes one of the following forms:

1) If the NDA is "complete," it will be approved, and may be marketed.

2) If the NDA is considered "incomplete" in certain specified respects (such as inadequate clinical data to demonstrate safety or efficacy), the manufacturer will be so informed. He may "complete" the application by submitting the lacking data.

Should the manufacturer disagree with the conclusions of the professional staff of the Bureau of Medicine, he may request conferences for discussion of the data which has been regarded as deficient. In case approval is still withheld, the manufacturer is entitled to an administrative hearing, if he chooses to protest the judgment. Furthermore, a negative ruling following a hearing may be appealed to the courts.

Antiobiotics and Insulin Preparations

New antibiotic drugs, and any new preparation of insulin, are also subject to the usual IND procedures. When the sponsor of an antibiotic considers the IND investigations sufficient evidence of a safe, effective product, he submits an Application for Certification which is reviewed by the Bureau of Medicine. For a new insulin product, he submits an NDA. After the antibiotic or insulin is "approved," a sample of each batch must be submitted by the manufacturer for tests to assure the identity, strength, quality, and purity of the product.

Surveillance of New Drugs on the Market

The responsibilities of the manufacturer do not end when a new drug has finally been approved for marketing. The manufacturer is required to send reports to the FDA every three months during the first year, every six months for the second year, and annually thereafter. These periodic reports must include information concerning current clinical studies, the quantity of the drug distributed, and copies of mailing pieces, labeling, and, if a prescription drug, advertising. Prompt reports (within fifteen days) are required of unexpected side effects, injury, toxicity or sensitivity reactions made known to the manufacturer. "Immediate" reports are required in case of drug mix-ups, evidence of contamination, or failure of the drug to exert its expected pharmacologic effect.