

The Drug Development Process II: Investigational New Drug Application

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The development of a new drug requires strict adherence to the Code of Federal Regulations, starting with the application for study of the compound in human subjects. Prior to a drug's entry into the clinic, pharmaceutical companies (hereafter referred to as *sponsors*) must test the drug candidate in specific ways in order to show with reasonable certainty that use in human subjects will be safe. On the basis of these preliminary evaluations, sponsors then file an investigational new drug application (IND) with the Food and Drug Administration (FDA), which will evaluate the preclinical information presented to determine if the stated safety of the candidate drug is reliable and sufficient to allow testing in humans.

This article, the second part of a 3-part series, provides an overview of the IND process, from sponsor screening of drugs to determine their suitability for application, through submission of the IND, to review by the FDA. The first article of the series provided a review of the process by which a newly synthesized compound becomes a pharmaceutical agent intended for patient use.¹

PRECLINICAL STUDIES

While a compound is being developed, substantial preclinical work must be performed to provide some degree of assurance that the candidate drug not only is safe for use in human subjects, but also is potentially efficacious and commercially viable. Although such assurances never carry absolute certainty, sufficient information usually is obtained from *in vitro* assays assessing mutagenicity and *in vivo* studies assessing whole animal toxicology and pharmacokinetics and can be used as a surrogate for evaluation purposes. These studies typically take several years to complete after initial identification from screening.² Such evaluations are performed in candidate drugs that show biologic effectiveness and potential efficacy in treating human disease conditions.

Thus, compounds must pass stringent requirements in order for an IND to be filed. The preparation of an IND typically entails several months of collation of doc-

umentation in the required format for agency submission. Whereas advances in screening technology have allowed for substantial numbers of compounds to be screened for biologic activity, it is estimated that, on average, only 1 in 5000 to 10,000 compounds will be considered for such an IND filing after screening.³

IND OVERVIEW

With the filing of an IND, the FDA becomes involved in the drug development process. The Center for Drug Evaluation and Research (CDER) is the review body for the FDA in the area of drug approval, whereas the Center for Biologics Evaluation and Research (CBER) evaluates biologics (eg, proteins). The Federal Food, Drug, and Cosmetic Act (amended by the FDA Modernization Act of 1997) defines the subject of the IND as a new drug subject to the specific requirements of the drug regulatory systems of both CDER and CBER.⁴ Clinical trials with the candidate drug generally can begin with IND filing, although the FDA has 30 days to review the application and may put any study already begun on clinical hold after reviewing submitted data on animal pharmacology/toxicology studies, manufacturing information, and clinical protocols and investigator information (**Table 1**).

The most common type of IND is the commercial IND, submitted by companies with the ultimate goal of gaining marketing approval for a candidate drug. There are, however, 3 types of noncommercial INDs⁵: investigator INDs, emergency use INDs, and treatment INDs. For the most part, application requirements are similar for commercial and noncommercial INDs, although certain types of cross-referencing (eg, referral to a commercial IND for specific parts of a noncommercial IND, such as the manufacturing section) can and do occur.

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Table 1. Key Components of an Investigational New Drug Application

Component	Description
Animal pharmacology and toxicology studies	Preclinical data providing information about experiments performed in experimental animals as well as in vitro studies that provide a toxicology profile
Manufacturing information	Information regarding the composition, manufacturing, and controls used to manufacture the candidate drug (information presented should ensure that the sponsor can adequately provide material for testing)
Clinical protocols and investigator information	Information on the manner and format of study ("study protocols") of the clinical evaluations proposed and on those who will be involved in the program (and their qualifications); commitments to obtain informed consent from research subjects, to have oversight and review of the clinical protocols by an institutional review board, and to adhere to regulations of the investigational new drug application

Investigator IND

Usually submitted by a physician, an investigator IND typically proposes to study either an unapproved drug or a drug that is approved but for which the physician intends an indication or patient population different than that previously approved by the FDA. The physician researcher who submits such an application both initiates and conducts the study and is responsible for both the direction of the study and the administration of the drug.

Emergency Use IND

The emergency use IND is employed by the FDA to authorize use of an experimental drug in an emergency situation when there is insufficient time to submit a standard IND under the usual strict guidelines.^{6,7} It can also be employed in situations in which patients do not meet the existing criteria for a specific study protocol or an approved study protocol does not exist.

Treatment IND

A treatment IND is submitted for use of a compound to treat a serious or life-threatening condition while the final clinical work is being performed and FDA review is taking place.

Table 2. FDA Review of an Investigational New Drug Application

Type of Review	Description
Medical	Assessment of clinical section in context of preclinical package
Chemistry	Issues related to drug identity, manufacturing control, and analysis
Pharmacology/toxicology	Description of drug's mechanism, pharmacologic effects in animals (pharmacokinetics), and toxicology
Statistical	Evaluation of methods and analysis of data
Safety	Composite review of safety of proposed research plan proposed

IND REVIEW PROCESS

As previously indicated, the IND details the research and preclinical work performed on a compound that suggest both potential efficacy in human disease and safety in subsequent human trials. In reviewing the application, the FDA conducts 5 reviews corresponding to sections of the IND: a medical review, a chemistry review, a pharmacology/toxicology review, a statistical review, and a safety review⁸ (Table 2).

The medical review is typically performed by a physician and involves the assessment of the clinical section of the submission. Toxicology information and any human pharmacology information are considered in the context of the clinical trial design, in order to determine the overall safety of that design. The clinical protocols are evaluated to determine the relative risks of administering the compound to human subjects, as well as whether the study design will provide the information necessary for understanding the safety and efficacy of the drug candidate. The statistical review is often combined with the medical review to provide information about the power of the proposed clinical trial and of the data provided in the preclinical package.

The chemistry review centers around the manufacturing and processing procedures involved in producing a drug candidate, ensuring that the compound to be tested can be reproducibly synthesized and remain stable. This step is obviously of particular relevance, because compounds that are unstable or not reliably pure pose a safety risk for human subjects. Moreover, candidate drugs for which an IND has been filed cannot be tested if the compound is not sufficiently identified.

The pharmacology/toxicology review evaluates the

preclinical and animal studies performed from which inferences can be drawn regarding the drug's potential effect in humans. Animal pharmacokinetic data in the application are also assessed. This review considers information on the pharmacologic effects and proposed mechanisms of action of the compound, as well as information on the drug's absorption, distribution, metabolism and excretion profiles. Information on toxicologic profiles also is required, with the extent of this information being dependent on the nature of the drug and the phase of human investigation. As previously implied, statistical review plays a part in this aspect of the review, providing an assessment of the methods used to collect and analyze the data.

After an initial review of the IND is performed, a composite safety review addressing the relative risks of the program and the completeness of the package information occurs. The FDA (CDER or CBER) has 30 calendar days to respond to an IND. In some cases, as mentioned previously, a clinical hold is placed because of a perceived risk or incompleteness of the data presented.⁷ If the FDA determines that a clinical hold is necessary, it will inform the sponsor that any clinical trial already in process must cease. Until the issue that prompted the clinical hold has been addressed, no current or additional clinical trials can be performed under the auspices of the IND in question. When the sponsor has addressed the issue(s) to the FDA's satisfaction, the clinical program can be started (or restarted). Subsequent clinical trials can begin immediately on submission of clinical protocols to the FDA; there is no 30-day waiting period for subsequent clinical trials after the submission of the first clinical trial protocol. Sponsors are required to update the FDA on the status of the IND on an annual basis, including any additional preclinical or clinical data that are available.

SUMMARY

The filing of an IND by a sponsor provides key preclinical and manufacturing information, as well as the planned clinical program for investigation of a candidate drug. The FDA reviews this information to determine the adequacy of information derived from experiments in animals and in vitro experiments alleging to show that there is reasonable safety in allowing administration of the drug to humans. The FDA also evaluates the clinical plan, to ensure that the study protocol(s) are designed in such a fashion that information regarding the safety and/or efficacy of the compound can be ascertained. The FDA has 30 days to review the IND and can either allow clinical studies to commence/continue or place a clinical hold on the program, asking the sponsor to address specific significant issues. With resolution of the issues, clinical trials can begin (or continue), and the clinical development program can ensue. **HP**

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