Abstract

In 2006, the U.S. Food and Drug Administration published its guide on exploratory investigational new drug (IND) studies with the goal of making the approach to early-stage, pilot clinical trials more flexible within the context of current regulations. The exploratory IND allows sponsors to initiate clinical trials of limited scale with reduced preclinical requirements. These studies may be important vehicles for the conduct of proof-of-principle pharmacodynamic investigations of highly potent molecules, for bioavailability studies that require only a single drug dose to be administered, and for imaging trials that permit critical dosimetry and biodistribution investigations of new molecules. These trials were done with no therapeutic intent and must be followed by traditional dose-escalation investigations that are supported by standard preclinical toxicologic and pharmacologic studies. To the extent that they allow early evaluations of essential drug characteristics that can only be obtained in humans, exploratory IND trials have the potential to limit the cost and improve the development times of new agents.

One of the most important goals of the Critical Path Initiative undertaken by the U.S. Food and Drug Administration (FDA) in 2004 was the reinvigoration of the pipeline of new pharmaceutical products entering the development cycle. The initiative recognized that the high cost and risk of early-phase drug and biological development were acting as barriers to entry for potential new therapies, and that these barriers might be part of the reason why fewer new products have been submitted for regulatory approval in recent years.

In January 2006, the FDA issued a guide on exploratory investigational new drug (IND) studies, citing the flexibility these regulations offered for early-phase drug development. The guide emphasized that the pharmaceutical industry should be taking greater advantage of exploratory studies to help overcome some of the time and cost challenges of drug development. In the view of the FDA, the use of the exploratory IND process would allow pharmaceutical companies and other drug developers to more quickly screen potential drug candidates and pinpoint those with the greatest promise. The FDA also noted that exploratory INDs could be especially beneficial for speeding up the development of products to treat cancer and other serious diseases.

The clear message being sent by the FDA is that sponsors can use the exploratory IND, combined with innovative preclinical testing that leverages advanced imaging and other technologies, to rapidly and safely assess new drugs and biologics. This approach would have the potential to reduce the time and cost of both preclinical testing and early-stage human trials, as well as more efficiently identify the best drug candidates to move forward into the traditional clinical trials process. The optimal result of this new approach may be a substantive increase (optimistically as much as a doubling) in the ultimate success rate of small-molecule drugs and biologics proceeding through late stage clinical trials, a success rate that is currently <10% (1). This issue of CCR Focus describes and discusses the application of the exploratory IND as the phase 0 concept (2–6).

Understanding Exploratory INDs

An exploratory IND study takes place early in phase I, before the costly safety, tolerance, and dose-escalation studies of a typical phase I program. It involves very limited human exposure to the drug candidate and has no therapeutic intent. Studies done under an exploratory IND can vary from single, subpharmacologic doses (microdose studies) to repeat-dose studies using pharmacologic exposures. A microdose study tests subpharmacologic doses (microdose studies) to repeat-dose studies using pharmacologic exposures. A microdose study tests subpharmacologic doses (microdose studies) to repeat-dose studies using pharmacologic exposures. A microdose study tests subpharmacologic doses (microdose studies) to repeat-dose studies using pharmacologic exposures. A microdose study tests subpharmacologic doses (microdose studies) to repeat-dose studies using pharmacologic exposures. A microdose study tests microdose exploratory IND studies can yield valuable data about a drug candidate, including (a) a drug’s pharmacokinetic properties, albeit only with the use of highly sensitive analytic techniques (7); (b) a product’s biodistribution characteristics using imaging technologies; or (c) whole-body,
organ, and tissue radiation dosimetry for investigational radio-labeled drugs or biologics. On the other hand, an exploratory IND can also support studies that use maximum doses that produce definite pharmacodynamic effects in human clinical trials, including dose levels that produce an exposure up to one-half of the area under the curve (AUC) at the no observed adverse effect level in the rodent. The preclinical development requirements for an exploratory IND, compared with a traditional IND, are outlined in Table 1 and are graphically depicted in Fig. 1. Important definitions are listed in Fig. 2.

The number of patients involved in these studies is small, usually fewer than the 30 or more patients required for a traditional phase I study. In addition, the duration of the human dosing period is brief, generally not more than 7 days. Because a limited number of patients are exposed to very small doses of the compound for a short period of time, the risk to patients is lower. Overall, the initial pharmacologic and toxicologic testing requirements are significantly reduced, as are patient recruiting costs.

The exploratory IND offers significant benefits for the numerous smaller companies that are performing much of the cutting-edge biopharmaceutical research today. It provides the ability to test potential compounds at a fraction of the cost of the traditional IND path, allowing a small company or academic investigator to conserve limited resources. It offers a path to more quickly compare investigational compounds allowing the identification of the most promising compound for continued development. It permits more rapid demonstration of proof of concept, which is critical for companies looking for investors to help them move their products forward to clinical development. Finally, the exploratory IND reduces the barrier to market entry for smaller research-based companies, which should lead to more new therapies.

The characteristics of exploratory INDs have added significance for companies developing treatments in therapeutic areas such as oncology and neurology, which can take advantage of sophisticated imaging technologies that can show proof of concept or mechanism of action at the low dosage levels required for exploratory studies.

Using Preclinical Testing to Enable Exploratory INDS

One of the most useful features of the exploratory IND is that the preclinical studies required to support such an IND can be closely tailored to the nature of the proposed investigational study. Thus, one of the essential features of a microdose study supported by an exploratory IND, that might be used for an imaging trial, for example, is that extended single-dose toxicity studies in animals can be used to support single dose studies in humans. For microdose studies, a single mammalian species can be used if justified by in vitro metabolism data. In addition, the route of exposure in animals should be the same as the intended route in humans. The study should be designed to establish a minimal toxic effect or large margin of safety (e.g., 100×). Scaling from animals to humans based on body surface area may be used to select the clinical dose. In these studies, animals should be observed for 14 days post-dosing, with an interim necropsy. Routine end points that should be evaluated include clinical signs, body weight, hematology and clinical chemistries, and histopathology. Because microdose studies involve only a single dose of microgram quantities, genetic toxicology and safety pharmacology testing are not required.

For exploratory IND trials designed to study the pharmacologic effects of candidate products, more extensive preclinical safety data would be required to support the safety of such studies. Because the goal would not include defining a maximally tolerated dose, however, the evaluation can still be less extensive than typically needed to support a traditional IND application. The critical preclinical information required includes a 2-week toxicology study in sensitive species (usually rodents) plus toxicokinetics, which should allow the no observed adverse effect level to be determined. In addition to studies in rodent species, additional studies in non-rodents were conducted to confirm that the rodent is a sensitive species. The number of dose administrations should be equal to the number of dosing days in a clinical trial. A single gender in the second species can be tested if no gender differences were observed in the rodent study, and if only a single sex will be studied in the exploratory IND trial. The number of animals

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Data from Pharmaceutical Research and Manufacturers of America presentation to the FDA, January 2004.
used in the confirmatory study may be fewer, but must be sufficient (e.g., at least four non-rodents) to rule out any possible toxicologic difference in sensitivity compared with the rodent.

Safety pharmacology testing is still required to support an exploratory IND. Central nervous system and respiratory assays can be done as part of a rodent toxicology study, whereas cardiovascular toxicity should be assessed in a non-rodent species, as defined in ICH S7A. In addition, each product should be tested for genotoxicity [bacterial mutation (Ames assay) and chromosomal aberrations] unless such testing is not appropriate for the population to be studied (such as terminally ill patients).

The results from the preclinical program can be used to select starting and maximum doses for the exploratory IND trials. The starting dose is anticipated to be ≤1/50th of the no observed adverse effect level from the 2-week toxicology study in the sensitive species on a mg/m² basis. The maximum clinical dose would be the lowest of the following: (a) one-quarter of the 2-week rodent no observed adverse effect level on a mg/m² basis; (b) up to one-half of the AUC at the no observed adverse effect level in the 2-week rodent study, or the AUC in the non-rodent species at the no observed adverse effect level for the rodent, whichever is lower; (c) the dose that produces a pharmacologic and/or pharmacodynamic response, or the dose at which target modulation is observed in the clinical trial; or (d) observation of an adverse clinical response. Escalation from the proposed maximal clinical dose should only be done after consultation with and concurrence by the FDA.

In addition to the substantial flexibility in studies of preclinical toxicology for the exploratory IND, there is also a streamlining of requirements for the production of the drug for human use. The guide emphasizes that the FDA intends that the expectations for details in manufacturing issues should always be scaled to the size of the clinical study and the stage of investigation. Furthermore, there are especial advantages for initial human studies when "the same batch of candidate product is used in both the toxicology studies and clinical trials."4

**Accelerating Portfolio Assessments**

The exploratory IND provides a much more cost-efficient approach than traditional phase I trials for sponsors who have several promising preclinical compounds for the same indication in a therapeutic portfolio. In the past, a sponsor typically would select just one product variation, based on pre-IND laboratory results, to move forward into phase I human testing because of the cost and time involved in preparing an IND and performing phase I trials, a process that typically takes 12 to 18 months. If the selected product did not perform as expected, the sponsor had to decide if it would be worth investing...
another 12 to 18 months and additional funds to test a second product variation from the portfolio. Using the exploratory IND process, a sponsor can take a completely different approach for portfolio testing. Because of the reduced requirements for pharmacology and/or toxicology testing, the preclinical costs are greatly decreased, and the process can be completed in as little as 3 to 4 months. Some of the differences in the requirements for supporting a conventional IND versus an exploratory IND are shown in Table 1.

Exploratory INDs can be leveraged for comparative testing of a therapeutic portfolio in two different ways, that is, horizontally or vertically. If a sponsor has several molecules or proteins in a portfolio, for example, the company could elect to move all of the therapies forward at the same time to gain as much clinical information as possible in the shortest period of time—a horizontal analysis. If a sponsor cannot afford to move multiple preclinical candidates forward at once, however, the company may elect to take a vertical approach to portfolio analysis. In this scenario, the sponsor ranks the candidates based on existing laboratory data and begins the exploratory IND process with the highest-rated (“most promising”) product. The sponsor can quickly evaluate the selected candidate’s potential and decide if it meets the expectations for proof of concept, method of action, or other criteria. If it does, the company can close the exploratory IND and move forward with that candidate immediately. If the first selected product does not perform adequately, the cost and time to reach that conclusion will be much less than the traditional IND process, and the second-ranked product in the portfolio can then be moved forward for analysis.

If the products have a similar target, the sponsor may be able to open a single exploratory IND encompassing several agents, which would further reduce both the development time and trial costs. Even if separate exploratory INDs are opened simultaneously, the cost to conduct the exploratory studies would still be substantially less than the cost of one traditional IND trial for a single compound. More important, the most promising candidate in the portfolio would be identified in just a few months, and the exploratory INDs for the less-promising candidates could be closed without further expenditure.

Recently, these two approaches for comparative portfolio assessment have been used successfully by both large and small pharmaceutical companies to quickly test preclinical compounds in humans and select the best candidates for additional trials, without undue patient risk or unreasonable levels of investment (8, 9).

Leveraging Imaging Technology for Comparative Analysis

The exploratory IND enables drug and biological developers to use comparative whole-body biodistribution and clearance imaging to accelerate the comparative analysis of a product portfolio. To accomplish the whole-body biodistribution imaging, the investigational product may be radiolabeled and then administered to enrolled subjects as part of the exploratory IND study. After administration, multiple whole-body images of the subject are taken at various time points to document the localization, passage, and clearance of the radiolabeled investigational product within the body. Table 2 provides examples of the vital information that can be derived from these biodistribution images. The goal of imaging studies comparing drug candidates is to find those that have the fastest or longest-lasting effect at the target site with the safest

Table 2. Types of data available from imaging trials conducted under the exploratory IND

- Demonstration of tumor localization, including residence time within the tumor
- Normal organ localization and organ retention
- Routes and rates of clearance through the kidneys and the liver


Fig. 2. Important definitions.
clearance rates and routes and the least effect on other organs. This targeting and safety data can play a key role in comparing potential products and identifying the most promising candidates to move forward in the clinical development process.

**Working with the FDA**

Successful use of exploratory INDs also requires a change in the way sponsors work with the FDA during the pre-IND process. The FDA guide makes it clear that every situation is different in determining what preclinical and early-human testing will be acceptable for exploratory INDS. A sponsor should begin working with FDA personnel early in the pre-IND and IND development process to discuss possible preclinical and clinical requirements for a particular compound, well before an IND is prepared or submitted.

A typical pre-IND discussion might involve a teleconference with FDA experts in pharmacology/toxicology, chemistry, manufacturing, and controls, and clinical development to discuss preclinical data, therapeutic targets, and potential clinical approaches. This meeting will provide the sponsor with valuable insight and guidance on the proposed clinical approach, as well as clarify the FDA’s expectations about the appropriate and acceptable data needed to support a specific compound, indication, and trial. By taking advantage of the pre-IND meeting process, a sponsor can greatly reduce the guesswork and risk of preparing an exploratory IND.

The use of exploratory IND studies, however, does not eliminate the need for a traditional IND or standard phase I human trials. Once the best drug candidate is found, the FDA expects the sponsor to close the exploratory IND and open a new IND that follows the traditional preclinical and clinical trial processes. This approach eliminates the less-promising candidates at a lower cost. The resources of the sponsor and the FDA are then concentrated on the compounds that are most likely to succeed, a change that should save time and money for everyone involved in drug development. Some of the perceived disadvantages in using this approach are listed in Table 1.

**Conclusion**

The essential message from the FDA is that existing regulations allow flexibility in the amount and types of data required for early-phase trials, depending on the goal of the trial and the anticipated risk to patients. The FDA believes that sponsors are not taking full advantage of that flexibility and, as a result, are providing much more preclinical data than the regulations require in many cases, resulting in higher costs that may be hampering product development. By leveraging the flexibility that is already available in FDA regulations for exploratory INDS, pharmaceutical companies can follow this more efficient approach to rapidly evaluate new drugs and biomolecules, reduce development costs, and bring effective therapies to market in a more timely manner, whereas improving patient safety.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

**References**

Leveraging Exploratory Investigational New Drug Studies to Accelerate Drug Development

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