The Role of Exploratory Investigational New Drugs for Translating Radiopharmaceuticals into First-in-Human Studies

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The Food and Drug Administration has provided a mechanism to reduce time and resources expended on new pharmaceuticals, including radiopharmaceuticals, in order to identify the most promising agents for further development. The exploratory investigational new drug guidance describes early phase 1 exploratory approaches involving microdoses of potential drug candidates that are consistent with regulatory requirements while maintaining the safety needed for human subjects, allowing sponsors to move ahead more quickly with the development of new agents.

Key Words: exploratory IND guidance; eIND; microdosing; 21 CFR Part 212; first-in-human RP

J Nucl Med 2015; 56:497–500
DOI: 10.2967/jnumed.114.146472

The U.S Food and Drug Administration (FDA) voiced its concerns in March 2004 that excessive development costs were preventing new life-saving drug products from reaching the patient at an affordable price (*1*). In its Critical Path document, the FDA asked why the tools of the last century were being used to develop drugs of the 21st century. The FDA's view was that "A new product development tool kit was urgently needed to improve predictability and efficiency along the critical path." This new product development mechanism would reduce the time and resources needed to separate those candidate drugs that hold promise from those that do not.

In June 2004, the European Medicines Agency Safety Working Party Position published a position paper that defined common standards of the nonclinical safety studies required to support human clinical trials of a single dose of a potential drug candidate administered at a microdose level (*2*). A microdose of the candidate drug was defined as less than 1/100th of the dose calculated to yield a pharmacologic effect of the test substance based on pharmacodynamic data obtained in vitro and in vivo and at a maximum dose of 100 μg or less. The clinical trials covered by this position paper were exploratory in nature and could be conducted with a single test candidate drug or with several closely related candidates.

In the United States, the FDA had originally published a guidance document in 1996 on single-dose acute toxicity testing for pharmaceuticals (*3*). That guidance was followed in 2004 by a draft guidance for industry, investigators, and reviewers, which was finalized in 2006. The guidance defined the microdose as less than 1/100th of the dose of a test substance calculated (based on animal data) to yield a pharmacologic effect for the test substance with a maximum dose of 100 μg or less or, for a protein product, 30 nmol or less (*4*). This document described which preclinical and clinical studies, as well as which chemistry, manufacturing, and controls information, should be considered when planning exploratory studies in humans. The eIND can be used for phase 0, or early phase 1, studies and involves limited human exposure. It cannot be used for therapeutic or diagnostic decision making or for safety or efficacy studies.

It would be most appropriate to use the eIND for first-in-human studies. It can be used to conduct preliminary clinical investigations of the mechanism of action and the pharmacokinetics of the investigational radiopharmaceutical. An eIND also allows for multiple candidate radiopharmaceuticals of the same chemical class to be evaluated on the basis of a single set of pharmacology–toxicology requirements. This approach requires less pharmacology and toxicology information, only a single species rather than the 2 species is required for a traditional investigational new drug (IND), reducing the overall cost. The goal for the initial studies in humans must be driven by the science and the need to minimize the risk through production control and preclinical safety and pharmacology studies.

At Washington University School of Medicine in St. Louis, we have 4 FDA-approved eIND applications, including a ^{64}Cu-labeled nanoparticle for imaging plaque; ^{18}F-nitric oxide synthase used to image cellular inducible nitric oxide synthase activity (*5*); ^{18}F-fluorbetaOx (*6*), a fluorinated fatty acid for measurement of myocardial fatty acid metabolism; and ^{18}F-*N*-[6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl-butyl]-2-(2-fluoroethoxy)-5-methyl-benzamide

Received Dec. 15, 2014; revision accepted Feb. 27, 2015.
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Published online Mar. 12, 2015.

(^{18}F-ISO-1). The first protocol submitted for the ^{18}F-ISO-1 eIND evaluated the σ-2 receptor status of patients diagnosed with lymphoma, breast, and head and neck cancer (*7*). The second protocol will examine ^{18}F-ISO-1 uptake in lung inflammation and cancer diagnosis.

REGULATORY APPROACHES: RADIOACTIVE DRUG RESEARCH COMMITTEE (RDRC), INDs, AND EINDs

Administration of research radiopharmaceuticals to humans is subject to FDA regulations. There are 2 mechanisms that can be used for human research involving radiopharmaceuticals: the RDRC application or the IND application, which includes the eIND.

The RDRC is defined in title 21 Code of Federal Regulations (CFR) part 361.1 (*8,9*). It is an institution-based committee that is approved by the FDA. The committee reviews and approves human research using a radioactive drug or biologic product (without an IND) when the research is basic science research and not intended for use in making clinical decisions. Basic research is intended to obtain essential information regarding metabolism (including kinetics, distribution, and localization) of a radiopharmaceutical, or regarding human physiology, pathophysiology, or biochemistry. The research cannot constitute a clinical trial and may not be used to determine the safety and effectiveness of a radioactive drug. The mass dose administered must be known not to cause any clinically detectable pharmacologic effect in humans, and the total amount of radiation administered must follow the guidelines outlined in 21 CFR part 361.1 (*8*).

If the research involves translation of a first-in-human radiopharmaceutical, it is necessary to submit an IND application to the FDA as defined in 21 CFR part 312 (*10*). However, if the clinical information desired meets the objectives of the eIND process and the amount of mass of the radiopharmaceutical that will be injected as the administered dose is a microdose (as defined above), then an eIND can be submitted instead of a traditional IND.

REGULATORY REQUIREMENTS FOR PRODUCTION OF RESEARCH RADIOPHARMACEUTICALS

To produce investigational radiopharmaceuticals for human use, it is necessary to follow the regulatory framework, either 21 CFR part 211 for SPECT (*11*) or 21 CFR part 212 for PET (*12*). Part 212 actually includes production requirements for investigational PET radiopharmaceuticals, used under an approved IND for phase 0, 1, or 2 studies or under an approved RDRC application, and allows use of either U.S. Pharmacopeia chapter <823> or part 212. Phase 3 PET studies must follow part 212.

SPECT radiopharmaceuticals in phase 0 and 1 studies can also be produced without following 21 CFR part 211, but the production during phase 1 must be compliant with the principles of current good manufacturing practices, which are defined in 21 CFR part 210 (*13*), and phase 2–3 must follow part 211.

COMPONENTS OF EIND OR IND

The sponsor of the IND application, in consultation with the physician investigator (if not the same person), is responsible for the development of the general investigational clinical plan and corresponding clinical protocols. For phase 0 to early phase 1 studies conducted under an eIND, the investigational plan is more limited in scope and number of subjects but may be more detailed in some areas than phase 2–3. For example, in a first-in-human study, more extensive safety monitoring (e.g., continuous electrocardiogram) may be collected because the goals of these early studies can include limited safety evaluation. Other eIND goals include biodistribution, mechanism of action, pharmacokinetics, dosimetry, imaging characteristics, dose determination, and exploratory efficacy. Additionally, the eIND goal can focus on selection of the most promising lead candidate radiopharmaceuticals.

Traditional IND phase 1–3 studies focus on the safety and effectiveness of the radiopharmaceuticals. Moving from the preliminary investigations of the candidate radiopharmaceutical under an eIND to the inclusion of safety and effectiveness requires submission of a traditional IND.

The investigator's brochure is a comprehensive document summarizing the body of information about an investigational product. The purpose of the brochure is to compile data relevant to studies in human subjects gathered during preclinical and other clinical trials and is not required for a sponsor-investigated IND for which the clinical investigations are conducted at a single study site.

The chemistry manufacturing and controls section is similar for both eIND and IND applications. Personnel should be trained in aseptic process and perform 3 medium fill-tests to simulate the procedure. This section should include a written procedure for the radiosynthesis, including all raw materials. Raw-material acceptance sheets should describe materials used and list specifications required to purchase and receive them. Materials should be segregated and secured for the human-use synthesis from routinely used chemicals or supplies in the laboratory. For the purchase of precursors for the synthesis, there should be an acceptance sheet including specifications such as the percentage purity required. It is recommended that a certificate of analysis be obtained when received. If precursors or nonradioactive standards are produced in-house, a written procedure should define the process. After synthesis, spectral data should be obtained for characterization of the compound, and the final product should be identified by the label, including the name of the compound, the lot number, and the date of production.

Quality control procedures are used to ensure the identity, strength, quality, purity, and potency of the final product, and quality control release specifications list the

test ranges allowed for release of the final radiopharmaceutical for human injection. The amount of mass allowable for the final product will be defined by the toxicology studies. For products that will be injected intravenously, the formulation will need to be sterile, which requires the setup of the final product vial in an International Organization of Standardization Class 5 environment and performance of appropriate environmental monitoring. Three validation runs, with full quality control testing for each batch, and stability testing for the 3 batches to determine the expiration time for the radiopharmaceutical are required.

Pharmacology and toxicology information is derived from preclinical safety testing performed in animals and in vitro. Pharmacologic studies can include target or receptor profiling and characterization of primary pharmacology in a relevant model. The toxicology evaluation recommended for the eIND is more limited than for a traditional IND application because microdose ($\leq$100 μg) studies are designed not to induce pharmacologic effects. For microdose toxicity studies, the FDA accepts a single mammalian species (both sexes), compared with the traditional IND, which requires 2 species. This reduced requirement results in significant cost reduction because a single toxicity study costs around $70,000–$110,000. The basis for the reduced preclinical package is the reduced scope of an eIND including the limited duration of drug exposure. Also the level of preclinical testing performed to ensure safety will depend on the scope and intended goals of the clinical trial. The toxicology evaluation should address known aspects of related drugs (e.g., liver toxicity) and the expected patient population as well as what is known about this specific drug. In some cases, when there is sufficient information about a class of compounds, a careful literature review can reduce the need for additional studies. The FDA recommends that toxicology studies are performed in a good laboratory practice laboratory. During pre-IND meetings with the FDA, the extent of nonclinical pharmacology–toxicology studies required can be discussed, to reduce nonessential studies. Also certain universities may have pharmacology or veterinary departments that are able to perform appropriate toxicology studies, and this could be discussed with the FDA. Additionally, the National Institutes of Health can offer assistance for certain toxicology studies (*14–16*).

The intended clinical route of administration should be used in the toxicology study. Animals should be observed for 14 d after dosing, with an interim necropsy typically on day 2, and endpoints evaluated should include body weights, clinical signs, clinical chemistries, hematology, and histopathology. To establish a margin of safety, the sponsor should demonstrate that a large multiple (e.g., 100 times) of the proposed human dose does not induce adverse effects in the experimental animals. Scaling from animals to humans should be based on body surface area. The objective of dosimetry estimates obtained from animal studies is to provide a preliminary assessment of the safety of the candidate radiopharmaceutical when administered to humans at the radioactivity dosages proposed in the research protocol. Typically, the FDA requires human dosimetry studies to be conducted as a component of the phase 0–1 study. A good laboratory practice laboratory is not required for these studies.

CONCLUSION

The eIND is the most appropriate route for first-in-human studies for conducting preliminary clinical investigations of the mechanism of action and pharmacokinetics of the investigational radiopharmaceutical and for evaluating multiple candidate radiopharmaceuticals of the same chemical class based on a single set of pharmacology–toxicology requirements. The RDRC allows only basic clinical investigations of radiopharmaceuticals when the chemical component has been previously administered to humans. The eIND offers the advantage of reduced regulatory requirements, including pharmacology–toxicology, from the traditional IND. The goal for the initial studies in humans must be driven by the science and by the need to minimize risk through production control and preclinical safety and pharmacology studies.

It is important to remember that a traditional IND submission is required to move the eIND radiopharmaceutical into phase 1–3 trials to evaluate the safety and effectiveness of a new radiopharmaceutical intended for diagnosis or therapy.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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