Microdose Radiopharmaceutical Diagnostic Drugs: Nonclinical Study Recommendations

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Pharmacology/Toxicology

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TABLE OF CONTENTS

I. INTRODUCTION 1

II. BACKGROUND 2

III. RECOMMENDATIONS FOR NONCLINICAL STUDIES 2

IV. CONCLUSION 4

Microdose Radiopharmaceutical Diagnostic Drugs: Nonclinical Study Recommendations Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to assist sponsors of microdose radiopharmaceutical diagnostic drugs on the nonclinical studies recommended to support human clinical trials and marketing applications.[2] This guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding regulation of this class of drugs and provides complementary recommendations to the guidance for industry, investigators, and reviewers *Exploratory IND (Investigational New Drug application) Studies* (exploratory IND guidance) and the ICH guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (ICH M3(R2)). This guidance discusses how to refine nonclinical study recommendations for this class of drug given its unique characteristics (e.g., microdose, radiolabeled, single (or infrequent) use, clinical use setting, and the Agency's nonclinical and clinical safety experience with these drugs).

This guidance also is intended to help sponsors facilitate the timely conduct of clinical trials, reduce the use of animals with the 3R (reduce/refine/replace) principles, and reduce the use of drug development resources. While both the exploratory IND and the ICH M3(R2) guidances describe recommended nonclinical studies intended to be conducted early in phase 1 exploratory

[1] This guidance has been prepared by the Division of Medical Imaging Products in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] As defined by the guidance for industry, investigators, and reviewers *Exploratory IND (Investigational New Drug application) Studies*, a microdose is defined as less than 1/100 of the dose of a test substance calculated (based on animal data) to yield a pharmacologic effect of the test substance with a maximum dose of less than or equal to 100 µg. The maximum dose for protein products is less than or equal to 30 nmol. This definition corresponds to approach 1 in Table 3: Recommended Nonclinical Studies to Support Exploratory Clinical Trials in the ICH guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

studies of microdose radiopharmaceutical diagnostic drugs, the guidances do not address what additional nonclinical studies are recommended for marketing approval. This guidance is intended to provide recommendations for a pathway to full drug development (marketing authorization) for microdose radiopharmaceutical diagnostic drugs.

As technology advances, microdose drugs that use new modalities may emerge. Although this guidance describes recommendations for current radiopharmaceutical diagnostic drugs, the general principles discussed could apply to new diagnostic drugs.

This guidance does not apply to radioactive drugs for research that are used in accordance with 21 CFR 361.1.[3] These issues are addressed in the guidance for industry and researchers *The Radioactive Drug Research Committee: Human Research Without an Investigational New Drug Application*.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

For radiopharmaceutical diagnostic drugs, the microdose evaluated during early clinical trials does not differ significantly from the microdose intended for marketing approval and is less than or equal to 100 µg. Because these diagnostic drugs are administered using a dose at the low end of the dose-response curve, dose-related adverse events are unlikely to occur. The Agency recommends that sponsors tailor the amount and type of nonclinical supporting data to account for the low potential for adverse events.

Because each drug is unique, the Agency encourages sponsors to consult the Division of Medical Imaging Products in the Center for Drug Evaluation and Research before submitting an IND and during drug development. If, at any stage of development, a sponsor determines that particular nonclinical pharmacology or toxicology studies are not needed and provides adequate justification in a waiver request, the Agency may grant a waiver for specific studies (21 CFR 312.10).

III. RECOMMENDATIONS FOR NONCLINICAL STUDIES

The Agency recommends that the sponsor schedule the nonclinical studies to facilitate the timely conduct of clinical trials (including appropriate safety monitoring based on findings in

[3] A radiolabeled compound without an IND can be administered at doses that are known to have no pharmacologic effect in humans when the compound has been studied in humans and the results of the studies have been published in the literature. These basic research studies should be conducted under the oversight of an institutional review board and a radioactive research committee (21 CFR 361.1).

nonclinical studies) and to reduce unnecessary use of animals and other resources. Nonclinical recommendations for microdose diagnostic radiopharmaceutical diagnostic drugs are listed in table below.

Table: Recommendations for nonclinical studies for microdose (≤ 100 µg) radiopharmaceutical diagnostic drugs

Study Type	Phase	Comments
Pharmacology	Before phase 1	These studies can include in vivo and in vitro pharmacologic characterizations (e.g., receptor/target/off-target profiling, imaging/radiation dosimetry studies). These studies should provide evidence that radiolabeling of unlabeled moiety does not significantly alter pharmacologic characterizations. The studies should be of sufficient sensitivity to rule out pharmacologic effects at the anticipated clinical dose.
Extended single-dose toxicity in one species (usually a rodent)	Before phase 1	FDA accepts the use of extended single-dose toxicity studies in animals to support single-dose clinical trials in humans. When a toxicity study is recommended, a sponsor can use a single mammalian species (both sexes). The route of exposure in animals should be the intended clinical route.* To establish safety margins, the sponsor should use a formulation that is as similar as possible to the formulation intended for use in clinical trials for marketing approval.**

continued

* In extended single-dose studies, animals should be observed for 14 days post-dosing with an interim necropsy, typically on day 2, and evaluated endpoints should include body weights, clinical signs, clinical chemistries, hematology, and histopathology (high dose and control only if no pathology is seen at the high dose). The sponsor should design the study to establish a dose inducing a minimal toxic effect or, alternatively, establishing a margin of safety. To establish a margin of safety, the sponsor should demonstrate that a large multiple of the proposed human dose (e.g., 100 times the human dose) does not induce adverse effects in the experimental animals. Scaling from animals to humans based on milligram per kilogram for IV or milligram per square meter for oral administration can be used to select the dose for use in the clinical trial. Scaling based on pharmacokinetic/pharmacodynamic modeling would also be appropriate if such data are available and the suggested dose does not exceed the dose determined from milligram per kilogram or milligram per square meter scaling.

** Bridging studies may be needed if changes in the formulation are apt to change the pharmacokinetics, the pharmacodynamics, or safety characteristics of the drug. A sponsor could use the cold compound or the decayed moiety of the labeled compound for these studies, when applicable.

Table, continued

Study Type	Phase	Comments
Genotoxicity	Not needed	The exploratory IND guidance states, "Because microdose studies involve only single exposures to microgram quantities of test materials and because such exposures are comparable to routine environmental exposures, routine genetic toxicology testing is not needed." This applies to any phase of clinical development when considering that the mass dose remains the same through marketing approval. Genotoxicity risk could be, by default, incorporated in labeling language regarding radiation exposure risk.
Safety pharmacology	Not needed	Safety pharmacology studies are not recommended because of the low subpharmacologic dose.
Repeat dose toxicity	Not needed	
Pharmacokinetic	Before phase 3	Information on pharmacokinetics (e.g., absorption, distribution, metabolism, excretion) in test species and in vitro biochemical information relevant to potential drug interactions should be available before exposing large numbers of human subjects to the investigational drug.
Developmental and reproductive toxicity	Waiver obtained as per § 312.10	With a waiver, these studies are not necessary because of the inherent radiation risk to the fetus from the radiopharmaceutical, which would be reflected in labeling.
Special toxicity	As per ICH M3(R2)	FDA does not recommend investigating IV local tolerance of a drug substance for microdose studies. The use of novel vehicles or excipients should be governed by applicable ICH and FDA guidances for industry.

IV. CONCLUSION

The recommendations in this guidance are intended to reduce the time and resources expended in microdose radiopharmaceutical diagnostic drug development without compromising patient safety. The clinical and nonclinical safety profiles of microdose radiopharmaceutical diagnostic drugs are critically important in the Agency's decision to tailor nonclinical recommendations for the safety profile of these diagnostic drugs. The Agency strongly recommends that the sponsor schedule a pre-IND meeting for evaluating the drug development recommendations for a specific drug.