Investigational Enzyme Replacement Therapy Products: Nonclinical Assessment

Guidance for Industry

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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Contains Nonbinding Recommendations

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I. INTRODUCTION

The purpose of this guidance is to help sponsors design and conduct nonclinical studies during development of investigational enzyme replacement therapy (ERT) products. Specifically, this guidance describes the Food and Drug Administration's (FDA's) current thinking about the substance and scope of nonclinical information needed to support initiation of clinical trials, ongoing clinical development, and marketing approval for investigational ERT products.

This guidance is intended as an adjunct to the ICH guidances for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010), *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals — Questions and Answers* (February 2013), and *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (May 2012).[2] These ICH guidances provide general recommendations about the nonclinical safety studies of traditional small molecule and biotechnology-derived pharmaceuticals that support human clinical trials, as well as marketing authorization for pharmaceuticals.

The recommendations in this guidance apply to ERT products indicated for lysosomal storage diseases and other diseases caused by inborn errors of metabolism. This guidance does not apply to the development of pancreatic enzyme products.

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

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

[2] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs.

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

ERT products are used to treat a wide array of rare inborn errors of metabolism disorders resulting from inheriting defective genes (e.g., Gaucher disease, Fabry disease, Pompe disease, and mucopolysaccharidoses). These diseases generally manifest early in life. The natural history varies within and across diseases. For a given disease, there may be multiple phenotypic presentations, which can range from rapidly progressing changes that result in early death or devastating irreversible morbidity within a very short time frame to a slower progressive course that can extend into adulthood. Treatments generally involve exogenously supplying the missing or defective protein.

Although an ERT product is intended to resemble the natural product as much as possible, the commercial protein is not produced endogenously and may not interact with the same target in the same way as the natural product. ERT products may be chemically modified for reasons such as extending half-lives or targeting delivery to specific sites such as the brain. Therefore, there is a potential for toxicities beyond hypersensitivity reactions (e.g., toxicity resulting from direct or indirect effects of excess enzyme levels or a possible toxic effect of the ERT to nontarget tissues). Given the wide array of clinical indications, variations in the natural history of disease, and enzyme product types, no single nonclinical program can be designed to fit all ERT products.

III. NONCLINICAL STUDY CONSIDERATIONS

A. Nonclinical Program Objectives

Nonclinical studies conducted to support clinical investigations for ERT products should address the following objectives:

- Pharmacodynamic characterizations, including proof-of-concept (POC) studies, to demonstrate functional enzyme replacement and identify biologically active dose levels

- Safety assessments, including toxicology studies, to inform selection of a safe starting dose, dose-escalation schedule, and dosing frequency; demonstrate the feasibility and safety of the investigational product's proposed clinical route of administration (ROA); and identify safety parameters that can guide clinical monitoring of safety in humans

B. Recommendations for Nonclinical Program Design

When planning the nonclinical development program, sponsors should consider the following issues that can affect the timing, duration, and type of supportive nonclinical studies needed to initiate clinical trials:

- The proposed clinical indication and population, such as whether children or adults will be studied, and the rate of disease progression to death or irreversible morbidity in that population

- Pharmacodynamic data, including changes in known disease-specific biomarkers that suggest the prospect of direct benefit to support first-in-human clinical trials in pediatric patients

- The availability of existing relevant nonclinical or clinical safety and pharmacology information for the specific ERT product under investigation

- The availability of existing relevant safety information about the proposed clinical delivery device or delivery procedure for the product, or with any related device or procedure, as appropriate

- The availability of appropriate species and models, either normal or enzyme deficient, for testing the investigational ERT product for the expected biological response with pathophysiology of the disease relevant to the target patient population

1. ERT Products Used in Nonclinical Studies

The investigational ERT product that will be administered in clinical trials should be used in the nonclinical studies that are used to determine a safe dose in humans. Sponsors should characterize each lot of an investigational ERT product used in the nonclinical studies according to prospectively established criteria, consistent with the stage of product development. Sponsors should also highlight and discuss in the investigational new drug application (IND) similarities and differences between the drug substance and the drug product intended for use in nonclinical studies and for clinical trials, including differences in excipients.

2. Selecting Animal Species

Sponsors should conduct nonclinical evaluations in relevant species. Assessing factors for determining a relevant species necessitates considering the specific ERT product and clinical indication. Some additional factors sponsors should consider when determining the most relevant species for testing ERT products include (1) comparability of molecular attributes, including the interspecies homology of the enzyme and the cell-surface receptors mediating uptake of the circulating ERT product; (2) distribution of the native enzyme and/or ERT product compared with that of humans; and (3) feasibility of using the planned clinical delivery system

or procedure, as appropriate. Sponsors should also justify the appropriateness of each animal species.[3]

3. Animal Models of Disease

Although studies in animal models of human diseases caused by single enzyme defects are not expected to replace clinical studies in humans, they can provide, in selected situations, complementary and supportive information that can facilitate the progression of a human ERT development program. The extent to which the information obtained from such animal models may be relevant to the human disease of interest depends on many factors. To this end, it is desirable that the selected animal disease model displays a phenotype that mimics to a large extent the clinical manifestations and the overall course of the human disease. Greater credibility and relevance can be given to animal data if the metabolic pathways and essential intermediary components are conserved between the selected animal species and humans. It is essential not only that the inactivated animal gene is the same as the human gene but also that the animal and human genes serve the same biological functions and that the metabolic pathways are preserved across species. If reliance on animal data is proposed, the IND should include information supporting the usefulness and/or ability of the models to mimic the target disease population.

Animal models of disease may provide proof of concept that the ERT of interest has the desired biological effect. They may also help identify a biologically effective dose or doses and dosing regimen or regimens and confirm the effectiveness of the animal dose through studies that measure reduction in tissue substrate levels or other related histopathological changes that can be linked mechanistically to the enzymatic defect. They can further provide evidence of biological activity by demonstrating improvement of the disease manifestations (including effects on survival).

In addition, studies in animal models can support future reliance on noninvasive biomarkers (e.g., disease-specific substrate levels and/or enzyme-reaction products in the circulation) as long as the rate and extent of improvement of the biomarker levels correlate with a reduction in tissue substrate deposition/tissue damage and/or improvements in organ function. Such biomarkers may later be used as pharmacodynamic markers of disease activity in humans in clinical trials and may even be qualified as surrogate markers.

If studies in animal models of disease are used to support the safety of an ERT product, sponsors should incorporate safety endpoints in the POC studies. FDA encourages sponsors to discuss the adequacy of study designs (e.g., number of animals used and plans for tissue collection and evaluation) with the review division before initiating the study.

[3] We support the principles of the 3Rs (reduce/refine/replace) for animal use in testing when feasible. FDA encourages sponsors to consult with review divisions when considering a nonanimal testing method believed to be suitable, adequate, validated, and feasible. FDA will consider if the alternative method could be assessed for equivalency to an animal test method.

4. Toxicology Studies

Sponsors should perform an appropriate nonclinical safety assessment to support the proposed clinical development program. Healthy animals represent the standard test system employed to conduct traditional toxicological studies. For studies to support ERT clinical trials, sponsors can consider study designs that use animal models of disease that incorporate important safety parameters that allow for assessing the potential toxicity of an investigational ERT product. Sponsors should consider POC studies in relevant animal disease models modified to assess toxicology endpoints prospectively, including microscopic examinations of tissues, as support for initiating human clinical trials. Using animal disease models for toxicity testing may also allow sponsors to detect toxicity caused by the interaction of the drug and the disease in ways that would not be observed in healthy animals. To obtain agreement on study design, sponsors should discuss such study designs with the review division before initiating a study.

The nonclinical safety assessment, whether conducted in healthy animals or in animal disease models, should be sufficiently comprehensive to permit identifying, characterizing, and quantifying potential local and systemic toxicities, their onset (i.e., acute or delayed), the effect of the product dose level on toxicity findings, and the possibility for reversing any toxicities (if applicable).

The overall design of the nonclinical studies should support the safety of the proposed clinical trial. Nonclinical toxicology study designs should include the following, as applicable:

- An adequate number of animals per sex that are appropriately randomized to each group. The number of animals needed will depend on existing safety concerns for the investigational ERT product, the species, the model, and the delivery system. If safety data are generated from POC studies to support clinical trials, sponsors should use an adequate number of animals to appropriately assess the safety endpoints. FDA recommends sponsors consult with the review division for design of these studies before initiating a study.

- Animals with the appropriate age and developmental status as related to the proposed clinical trial population. When a first-in-human clinical trial for an ERT product will enroll pediatric patients, sponsors should conduct toxicity studies that use juvenile animals before initiating a clinical trial. The major issue is the potential for adverse effects on the developing organ systems in young pediatric patients (e.g., central nervous system, reproductive tract, immune system, and skeletal system). ICH M3(R2) and the guidance for industry *Nonclinical Safety Evaluation of Pediatric Drug Products* (February 2006) provide recommendations for determining the need for juvenile animal studies. Sponsors can submit the protocol for the juvenile animal toxicology studies to the review division for the division's concurrence on appropriate toxicology endpoints before conducting the study. The juvenile animal toxicity studies potentially may be waived when (1) clinical development is initiated in adult patients, (2) there are no specific safety concerns from studies in adult animals or adult patients, and (3) target organs with identified toxicity concerns are not undergoing development at the time of treatment.

- Appropriate control groups. A control group should be included in all toxicology studies with ERT products. An appropriate control group should be age-matched animals that have been administered the formulation vehicle only. When it is necessary to co-administer an antihistamine (e.g., diphenhydramine) to control hypersensitivity reactions to the ERT product, sponsors should include in the study a vehicle control group and a vehicle-plus-antihistamine control group. Sponsors should also provide justification for the specific control group or groups selected.

- Appropriate dose levels. Results obtained from POC studies should guide selection of the target dose levels both for nonclinical safety assessment and for clinical development. ICH M3(R2) and its subsequent questions-and-answers document provide considerations for selecting high doses for general toxicity studies. In general, in the absence of frank toxicity, the exposure at the highest doses tested for ERT products should be severalfold greater than the exposure expected at the highest proposed clinical dose regimen. The highest dose level used in nonclinical studies may be restricted because of animal size, tissue volume or size, ROA, or product-manufacturing capacity. Sponsors should provide justification, with supporting data, for the specific dose levels selected.

- The dosing schedule should reflect the expected clinical exposure, to the extent possible.

- An adequate duration of dosing. Decisions regarding the dosing duration in the nonclinical studies conducted to support first-in-human dosing of ERT products should consider two key issues: (1) the treatment of diseases caused by inborn errors of metabolism is expected to be chronic, and the first-in-human clinical trials are generally expected to be chronic dosing studies; and (2) greater uncertainty about risk may be acceptable in the setting of a disease with a rapid course to death or irreversible morbidity. For these reasons, sponsors should not only design the nonclinical study plan to support chronic dosing in patients who enter the first-in-human clinical trial but also consider the disease phenotype of the patients who will be enrolled in the trial.

  If the clinical trial entry criteria define a phenotype that is anticipated to progress rapidly to irreversible morbidity or mortality over the course of approximately 1 year, then repeat-dose toxicology studies in a rodent and a nonrodent species of 1-month dosing duration may be sufficient to initiate clinical trials. Initial dosing in these patients can also be supported by POC studies of appropriate duration in animal disease models, with adequate toxicological assessments. A 3-month toxicity study in one species may be needed before submission of a marketing application. Three-month studies in two species may be needed if the toxicological findings of the 1-month studies in the rodent and the nonrodent are not similar. Sponsors could conduct the 3-month toxicity study or studies in parallel with the first-in-human clinical trial. In the event of severe toxicity, including recovery animals can provide useful information.

  If the clinical trial entry criteria define a phenotype that would be expected to have slower disease progression, then toxicology studies of at least 3 months' duration in a rodent and a nonrodent species will be needed to initiate first-in-human clinical trials; this is

because, given the chronic nature of these rare diseases and unmet medical need, first-in-human clinical trials may be anticipated to initiate chronic dosing.

In cases for which short-term clinical dosing (e.g., less than 1 month) is proposed and considered appropriate, shorter-duration toxicology studies may be acceptable as discussed in ICH M3(R2). Sponsors should complete longer-duration toxicology studies to support chronic clinical dosing as discussed above.

- An ROA that mimics the intended clinical route as closely as possible. If the delivery device could impact toxicology, then we recommend sponsors use the delivery device intended for use in the clinical trials to administer the investigational ERT product in the definitive toxicology studies if possible. If it is not possible to replicate the clinical ROA in the animal model, then sponsors should propose and scientifically justify alternative routes or methods as a part of the nonclinical development plan.

- Safety endpoints that capture potential toxicities. Standard parameters evaluated should include mortality (with cause of death determined, if possible), clinical observations, body weights, physical examinations, food consumption, clinical pathology (serum chemistry, hematology, coagulation, urinalysis), organ weights, gross pathology, and histopathology. Additional developmental endpoints may be appropriate when conducting juvenile animal studies.

- Assessment of the effect of antidrug antibodies (ADA) on drug exposure and in response to the administration of the ERT product. This information is needed to assess the effect of ADA formation on the interpretation of the toxicology study findings.

These nonclinical data can help guide first-in-human dose selection. For example, data generated from the toxicology studies may establish a no observed adverse effect level, which can help sponsors select the starting dose level for the clinical trial. Alternatively, sponsors can consider a minimum efficacious dose (MED), as predicted by a relevant animal disease model, when selecting a starting dose. In addition, this information may allow sponsors to avoid or mitigate significant toxicities in patients.

5. Good Laboratory Practice

According to 21 CFR 312.23, each toxicology study intended primarily to support the safety of a proposed clinical investigation is subject to good laboratory practice (GLP) regulations under 21 CFR part 58. However, some toxicology assessments, although of sufficient quality and integrity, may not fully comply with the GLP regulations. For example, toxicology data for investigational ERT products are sometimes collected in POC studies that may use an animal model of disease requiring unique animal-care issues and technical expertise unavailable at a GLP testing facility. If the study is not conducted in compliance with GLP regulations, sponsors must include in the final study report a brief statement about the reason for the noncompliance (21 CFR 312.23(a)(8)(iii)). In addition, sponsors need to demonstrate that non-GLP studies submitted to support safety of an investigational ERT product are rigorous and adequately controlled to maintain reliability, quality, and integrity.

All nonclinical studies that incorporate safety parameters in the study design should be conducted using a prospectively designed study protocol. Results derived from these studies should be of sufficient quality and integrity to support the proposed clinical trial. Sponsors should include in the nonclinical study report a summary of all deviations from the prospectively designed study protocol and their potential effect on study integrity and outcome.

6. Product Development for Later-Phase Clinical Trials and Marketing Applications

As development of an investigational ERT product progresses to later-phase clinical trials, sponsors should consider conducting additional nonclinical studies to address any outstanding issues. For example, if manufacturing or formulation changes occur such that comparison of the later-phase ERT product with the product used in early-phase clinical trials is uncertain, sponsors may need additional in vitro and/or in vivo nonclinical studies to bridge the two products. Such bridging studies allow data collected with the early-phase product to support later-phase development or licensure. Additional nonclinical studies might be warranted if the ROA or patient population changes significantly from the early-phase clinical trials.

Toxicity studies of 3 months' duration generally should be considered sufficient to support a marketing application for an ERT product. However, if the 3-month toxicity studies reveal concerning findings, then FDA may recommend toxicity studies up to 6 months' duration to address outstanding concerns. In general, we recommend conducting a battery of reproductive toxicity studies, as described in the ICH guidance for industry *S5(R2) Detection of Toxicity to Reproduction for Medicinal Products: Addendum on Toxicity to Male Fertility* (April 1996) (refer to ICH M3(R2) regarding the timing of these studies). However, flexibility in timing or requirements for specific studies may be warranted in certain cases with adequate justification. Certain studies can be waived or delayed until after approval of the marketing application depending on the indicated patient population.

Genotoxicity studies are not considered applicable to ERT products, so FDA does not recommend these studies. Evaluating carcinogenic potential generally is not needed to support a marketing application. However, chemically modified ERT products (e.g., a recombinant human enzyme conjugated with a chemical linker) may need an assessment to address the potential for genotoxicity and/or carcinogenicity.

7. Nonclinical Study Reports

Sponsors should submit a report for each in vitro and in vivo nonclinical study intended to demonstrate the safety of an investigational ERT product. Complete reports of pharmacology and POC studies generally are not required for an IND; however, sponsors should submit complete study reports if the POC studies with safety information are used to support clinical trials. Each complete study report should include, but not be limited to, the following: (1) a prospectively designed protocol and listing of all protocol amendments; (2) a detailed description of the study design (e.g., the test system used, animal species or model used, control and investigational products administered, dose levels, detailed procedures for product administration, and collection of all study protocol parameters); (3) complete data sets for all

parameters evaluated, including individual animal data and tabulated/summary data; and (4) analysis and interpretation of the results obtained.

8. Communicating with CDER Pharmacology/Toxicology Staff

We recommend sponsors communicate with the Center for Drug Evaluation and Research (CDER) pharmacology/toxicology staff of the relevant review division, through the division project management staff, early in the investigational ERT product development program. Nonclinical testing programs for ERT products often need to be highly individualized; therefore, discussions with the review division may be needed regarding CDER expectations for the specific product and indication. If sponsors plan to leverage toxicology information obtained from the POC study to support initiating the first-in-human clinical trial, a pre-IND meeting with the review division to discuss design of the POC study before its initiation improves the chances that the study data will be adequate to support first-in-human clinical trials. This interaction can serve to facilitate more rapid access to treatment for patients.