Investigational Enzyme Replacement Therapy Products: Nonclinical Assessment Guidance for Industry

DRAFT GUIDANCE

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I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the design and conduct of nonclinical studies during development of investigational enzyme replacement therapy (ERT) products. Specifically, this guidance addresses the Food and Drug Administration’s (FDA’s) current thinking regarding 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, M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals — Questions and Answers, and S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals. These ICH guidances provide general recommendations regarding the nonclinical safety studies of traditional small molecules and biotechnology-derived pharmaceuticals that support human clinical trials, as well as marketing authorization for pharmaceuticals. As noted in ICH M3(R2), “Pharmaceuticals under development for indications in life-threatening or serious diseases (e.g., advanced cancer, resistant human immunodeficiency virus (HIV) infection, and congenital enzyme deficiency diseases) without current effective therapy also warrant a case-by-case approach to both the toxicological evaluation and clinical development in order to optimize and expedite drug development.”

1 This guidance has been prepared by the Division of Gastroenterology and Inborn Errors Products in the Center for Drug Evaluation and Research (CDER) 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 Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.
This guidance provides specific recommendations regarding the nonclinical safety evaluation of ERT products and assists sponsors in designing an appropriate nonclinical program to support clinical investigation and submission of a marketing application.

Historically and with few exceptions, ERT products have been developed to treat lysosomal storage diseases. The recommendations in this guidance are applicable to ERT products indicated for either lysosomal storage diseases or other diseases related to inborn errors of metabolism. However, this guidance is not applicable to the development of pancreatic enzyme products (see the guidance for industry Exocrine Pancreatic Insufficiency Drug Products — Submitting NDAs).

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

ERT products are used to treat a wide array of rare inborn errors of metabolism disorders resulting from the inheritance of defective genes (e.g., Gaucher disease; Fabry disease; Pompe disease; mucopolysaccharidoses I, II, IIIA and B, IVA, and VI). These diseases generally manifest early in life. The natural history varies across and within diseases. Multiple phenotypic presentations may exist in one disease, and the phenotypes can range from indolent, progressive degenerative disorders to rapidly progressing disease that results in death or devastating irreversible morbidity within a very short time frame. Treatments generally involve exogenously supplying the missing or defective protein.

A treatment designed to replace an endogenous protein might be expected to be associated with toxicities limited primarily to hypersensitivity reactions; however, the delivery of the product does not always mimic the pathway by which the protein is produced endogenously. Therefore, the potential exists for safety issues other than hypersensitivity reactions (e.g., toxicity resulting from direct or indirect effects of excess enzyme levels or possible toxicity of the ERT to non-target tissues). Given the wide array of clinical indications, natural history of disease, and product types, no single nonclinical program can be designed to address all ERT products.

III. NONCLINICAL STUDY CONSIDERATIONS

A. Nonclinical Program Objectives

Nonclinical studies conducted to support clinical investigations for ERT products should address these objectives:
Pharmacodynamic characterizations, including proof-of-concept (POC) studies, should demonstrate biological plausibility and identify biologically active dose levels.

Safety assessments, including toxicology studies, should 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 General 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 progression of the disease to death or irreversible morbidity in that population. Pharmacodynamic data that suggest the prospect of direct benefit, which should be considered in evaluating risk, are of key importance to support first-in-human trials that will enroll pediatric patients.

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

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

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

1. Investigational ERT Products Used in Nonclinical Studies

The investigational ERT product that will be administered to the patient population should be used in the pivotal nonclinical studies (i.e., studies used to determine a safe dose in humans). Each lot of an investigational ERT product used in the nonclinical studies should be characterized according to prospectively established criteria, consistent with the stage of product development. Similarities and differences between the drug substance and drug product intended for use in nonclinical studies and for clinical trials, including differences in excipients, should be highlighted and discussed in the investigational new drug application (IND). The safety of all ingredients should be supported for the intended clinical use.
2. Selection of Animal Species

Nonclinical evaluations should be conducted in relevant species. Assessment of factors for determining a relevant species necessitates consideration of the specific ERT product and clinical indication. Some additional factors that should be considered when determining the most relevant species for testing of 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 in humans; (2) the distribution of the native enzyme and/or ERT product compared to that of humans; (3) immune tolerance to the ERT product; and (4) feasibility of using the planned clinical delivery system or procedure. The sponsor should provide a justification of the appropriateness of each animal species.

3. Animal Models of Disease

Pharmacologic activity of an ERT may be difficult or impossible to detect in animals with normal levels of the endogenous enzyme targeted for replacement. For example, dosing of the ERT to animals with normal endogenous enzyme levels may result in excessive levels of enzyme as well as toxicities that are unlikely to occur in the intended patient population. Thus, studies conducted in animal disease models deficient in the targeted enzyme are preferable to using healthy animals in assessing the pharmacodynamic activity — and, in some cases, the toxicology — of ERT products. Nonclinical studies conducted in animal models of disease may also provide insights regarding species relevancy and the relationship of dose to activity. In addition, use of animal disease models provides the opportunity for possible identification of biomarkers that may be applicable for monitoring in clinical trials.

The potential limitations of animal models of disease should be recognized. A publication by Morgan et al. (2013) provides a detailed discussion of the technical challenges and considerations for the use of animal disease models in safety studies. When animal disease models are used in studies to support the clinical usefulness and safety of an ERT product, the IND should include information supporting the usefulness and/or ability of the model(s) to mimic the target disease population and to permit assessment of the safety of the investigational ERT product, taking into account each of the following:

- The similarities and differences between the pathophysiology of the disease in the animal model and the disease in humans
- Animal models of disease may demonstrate increased susceptibility to the effects of the investigational ERT versus healthy animals
- Possible exacerbation of an existing disease condition or induction of toxicity in response to the investigational ERT

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4. Proof-of-Concept Studies

Nonclinical POC studies of ERT in animal disease models are encouraged. These studies can address the objective of establishing biological plausibility before first use in humans. These studies, when designed appropriately, also can be used for assessment of toxicity and to support safety in clinical trials (see section III.B.5). Such studies may also help identify biologically active dose levels and inform a suitable dose-escalation schedule and dosing frequency. The animal model(s) selected for assessment should demonstrate a biological response to the investigational ERT similar to that expected in humans to be informative in support of clinical trials. Pharmacologic activity can be demonstrated through studies that measure tissue substrate levels in animals deficient in (or lacking) the targeted enzyme following treatment with the ERT. In addition, the detection of enzyme-reaction products in the circulation can also serve as evidence of pharmacologic activity.

Nonclinical in vitro assays intended to assess aspects of the biological activity of an investigational ERT product can provide supporting POC information. In vitro studies can be useful for demonstration of pharmacodynamic activity (e.g., substrate clearance) or the estimation of intracellular half-life of ERTs for lysosomal storage diseases. However, in vitro testing alone is not sufficient to reliably anticipate the outcome of physiological and biologic activity of the product following in vivo administration. Accordingly, the nonclinical testing program should incorporate both in vitro and in vivo approaches to achieve an understanding of the biological plausibility for use of the investigational ERT in the intended patient population.

Sponsors are encouraged to incorporate safety endpoints in POC studies and should discuss the adequacy of study designs (e.g., number of animals used and comprehensive tissue collection and evaluation) with the review division before study initiation.

5. Toxicology Studies

An appropriate nonclinical safety assessment should be performed 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 assessment of the potential toxicity of an investigational ERT. POC studies in relevant animal disease model(s) modified to prospectively assess toxicology endpoints, including microscopic examinations of tissues, should be considered as support for initiation of human clinical trials. The use of animal disease models for toxicity testing may also allow for detection of toxicity caused by the interaction of the drug and the disease in ways that would not be observed in healthy animals. Sponsors should discuss such study designs with the review division before study initiation to obtain agreement on study design.

The nonclinical safety assessment, whether conducted in healthy animals or animal disease models, should be sufficiently comprehensive to permit identification, characterization, and quantification of 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 reversal of any toxicities (if warranted).
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 can vary depending 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 consider the use of an adequate number of animals for these studies. Consultation with the review division is recommended for design of these studies before study initiation.

- Animals with the appropriate age and developmental status as related to the proposed clinical trial population. When a first-in-human trial for an ERT will enroll pediatric patients, toxicity studies that use juvenile animals should be conducted before clinical trial initiation. 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 provide recommendations for determination of 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 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 example of an appropriate control group includes age-matched animals administered the formulation vehicle only. When it is necessary to co-administer an antihistamine (e.g., diphenhydramine) to control hypersensitivity reactions to the ERT, the study should include a vehicle control group and a vehicle plus antihistamine control group. Justification should be provided for the specific control group(s) selected.

- Appropriate dose levels. Results obtained from POC studies should guide selection of the target dose levels for both nonclinical safety assessment and for clinical development. ICH M3(R2) and its subsequent questions and answers document provide considerations for selection of high doses for general toxicity studies. In general, the highest doses tested for ERT products should at least achieve some multiple of exposure over 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. Justification, with supporting data, should be provided for the specific dose levels selected.

- A dosing schedule that reflects the expected clinical exposure, to the extent possible.
An adequate duration of dosing. Decisions regarding the duration of dosing in the nonclinical studies conducted to support first-in-human dosing of ERT products should be based on two key issues: (1) the treatment of diseases caused by inborn errors of metabolism is expected to be chronic, and limiting treatment in first-in-human trials to short-term use generally is not acceptable when there are no available therapies; and (2) greater uncertainty regarding risk may be acceptable in the setting of a disease with a rapid course to death or irreversible morbidity. For these reasons, the nonclinical study plan should be designed to support chronic dosing in patients who enter the first-in-human trial, while also taking into consideration the disease phenotype of the patients who will be enrolled in the trial.

If the entry criteria define a phenotype that can be expected to rapidly progress to death or substantive irreversible morbidity over the course of 1 year, then repeat-dose toxicology studies in a rodent and a non-rodent 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, conducted with adequate toxicological assessments. A 3-month toxicity study in one species is needed to support approval of the ERT product for the rapidly progressing disease phenotype. Two species may be needed if the toxicological findings of the 1-month studies in the rodent and the non-rodent are not similar. The 3-month toxicity study or studies should be conducted in parallel with the first-in-human trial.

If the clinical trial entry criteria define a phenotype that would be expected to have slower disease progression, then toxicology studies in a rodent and a non-rodent species of at least 3 months’ duration will be needed to initiate first-in-human trials; this is because, given the chronic nature of these rare diseases, and unmet medical need, chronic dosing would be expected to start with first-in-human exposures.

In cases where 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). Longer duration toxicology studies should be completed to support chronic clinical dosing as discussed above.

An ROA that mimics the intended clinical route as closely as possible. Whenever possible, the delivery device intended for use in the clinical trials should be used to administer the investigational ERT product in the definitive toxicology studies. If it is not possible to replicate the clinical ROA in the animal model, then alternative routes or methods should be proposed and scientifically justified 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 or appetite, water consumption (as applicable), 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 exposure and 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 clinical trial design. For example, data generated from the toxicology studies potentially may establish a no observed adverse effect level, which can help determine selection of the starting dose level and subsequent dose-escalation scheme for the clinical trial. In addition, this information potentially may allow for circumvention or mitigation of significant toxicities in patients.

6. **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 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, a brief statement of the reason for the noncompliance must be submitted in the final study report (21 CFR 312.23(a)(8)(iii)). In addition, the sponsors need to demonstrate that non-GLP studies submitted to support safety of an investigational ERT are rigorous and adequately controlled to maintain uniformity, consistency, reliability, reproducibility, 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. A summary of all deviations from the prospectively designed study protocol and their potential effect on study integrity and outcome should be provided in the nonclinical study report.

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

As development of an investigational ERT product progresses to later-phase clinical trials, consideration should be given to the conduct of additional nonclinical studies to address any outstanding issues. For example, if manufacturing or formulation changes occur such that the comparability of the later-phase ERT product to the product used in early-phase clinical trial(s) is uncertain, additional in vitro and/or in vivo nonclinical studies may be needed 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. However, if the 3-month toxicity studies reveal concerning findings, then toxicity studies up to 6 months duration may be recommended to address any outstanding concerns. In general, we recommend conducting a battery of reproductive toxicity
8. **Nonclinical Study Reports**

A report should be submitted 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, complete study reports should be submitted 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.

9. **Communication With CDER Pharmacology/Toxicology Staff**

We recommend communication 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 the sponsor plans to leverage toxicology information obtained from the POC study to support initiation of the first-in-human trial, a pre-IND meeting with the review division to discuss design of the POC study before its initiation optimizes the chances that the study data will be adequate to support first-in-human trials. This interaction can serve to facilitate more rapid access to treatment for patients.