
Investigational Enzyme Replacement Therapy Products: Nonclinical Assessment 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DRAFT GUIDANCE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)**

**May 2015
Pharmacology and Toxicology**

Investigational Enzyme Replacement Therapy Products: Nonclinical Assessment Guidance for Industry

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2 **Products: Nonclinical Assessment**
3 **Guidance for Industry¹**
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8 This draft guidance, when finalized, will represent the current thinking of the Food and Drug
9 Administration (FDA or Agency) on this topic. It does not create any rights for any person and is not
10 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the
11 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible
12 for this guidance as listed on the title page.
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17 **I. INTRODUCTION**
18

19 The purpose of this guidance is to assist sponsors in the design and conduct of nonclinical studies
20 during development of investigational enzyme replacement therapy (ERT) products.
21 Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current
22 thinking regarding the substance and scope of nonclinical information needed to support
23 initiation of clinical trials, ongoing clinical development, and marketing approval for
24 investigational ERT products.
25

26 This guidance is intended as an adjunct to the ICH guidances for industry *M3(R2) Nonclinical*
27 *Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for*
28 *Pharmaceuticals*, *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials*
29 *and Marketing Authorization for Pharmaceuticals — Questions and Answers*, and *S6(R1)*
30 *Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*.² These ICH
31 guidances provide general recommendations regarding the nonclinical safety studies of
32 traditional small molecules and biotechnology-derived pharmaceuticals that support human
33 clinical trials, as well as marketing authorization for pharmaceuticals. As noted in ICH M3(R2),
34 "Pharmaceuticals under development for indications in life-threatening or serious diseases (e.g.,
35 advanced cancer, resistant human immunodeficiency virus (HIV) infection, and congenital
36 enzyme deficiency diseases) without current effective therapy also warrant a case-by-case
37 approach to both the toxicological evaluation and clinical development in order to optimize and
38 expedite drug development."
39

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>.

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40 This guidance provides specific recommendations regarding the nonclinical safety evaluation of
41 ERT products and assists sponsors in designing an appropriate nonclinical program to support
42 clinical investigation and submission of a marketing application.

43
44 Historically and with few exceptions, ERT products have been developed to treat lysosomal
45 storage diseases. The recommendations in this guidance are applicable to ERT products
46 indicated for either lysosomal storage diseases or other diseases related to inborn errors of
47 metabolism. However, this guidance is not applicable to the development of pancreatic enzyme
48 products (see the guidance for industry *Exocrine Pancreatic Insufficiency Drug Products —*
49 *Submitting NDAs*).

50
51 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.
52 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only
53 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
54 the word *should* in Agency guidances means that something is suggested or recommended, but
55 not required.

56
57

58 **II. BACKGROUND**

59

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

68

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

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78 **III. NONCLINICAL STUDY CONSIDERATIONS**

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80 **A. Nonclinical Program Objectives**

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82 Nonclinical studies conducted to support clinical investigations for ERT products should address
83 these objectives:

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- 87
- 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
- 92

93

B. Recommendations for General Nonclinical Program Design

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95

96 When planning the nonclinical development program, sponsors should consider the following

97 issues that can affect the timing, duration, and type of supportive nonclinical studies needed to

98 initiate clinical trials:

99

- 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.

116

1. Investigational ERT Products Used in Nonclinical Studies

118

119 The investigational ERT product that will be administered to the patient population should be

120 used in the pivotal nonclinical studies (i.e., studies used to determine a safe dose in humans).

121 Each lot of an investigational ERT product used in the nonclinical studies should be

122 characterized according to prospectively established criteria, consistent with the stage of product

123 development. Similarities and differences between the drug substance and drug product intended

124 for use in nonclinical studies and for clinical trials, including differences in excipients, should be

125 highlighted and discussed in the investigational new drug application (IND). The safety of all

126 ingredients should be supported for the intended clinical use.

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128 2. *Selection of Animal Species*
129

130 Nonclinical evaluations should be conducted in relevant species. Assessment of factors for
131 determining a relevant species necessitates consideration of the specific ERT product and clinical
132 indication. Some additional factors that should be considered when determining the most
133 relevant species for testing of ERT products include: (1) comparability of molecular attributes,
134 including the interspecies homology of the enzyme and the cell surface receptors mediating
135 uptake of the circulating ERT product in humans; (2) the distribution of the native enzyme
136 and/or ERT product compared to that of humans; (3) immune tolerance to the ERT product; and
137 (4) feasibility of using the planned clinical delivery system or procedure. The sponsor should
138 provide a justification of the appropriateness of each animal species.
139

140 3. *Animal Models of Disease*
141

142 Pharmacologic activity of an ERT may be difficult or impossible to detect in animals with
143 normal levels of the endogenous enzyme targeted for replacement. For example, dosing of the
144 ERT to animals with normal endogenous enzyme levels may result in excessive levels of enzyme
145 as well as toxicities that are unlikely to occur in the intended patient population. Thus, studies
146 conducted in animal disease models deficient in the targeted enzyme are preferable to using
147 healthy animals in assessing the pharmacodynamic activity — and, in some cases, the toxicology
148 — of ERT products. Nonclinical studies conducted in animal models of disease may also
149 provide insights regarding species relevancy and the relationship of dose to activity. In addition,
150 use of animal disease models provides the opportunity for possible identification of biomarkers
151 that may be applicable for monitoring in clinical trials.
152

153 The potential limitations of animal models of disease should be recognized. A publication by
154 Morgan et al. (2013) provides a detailed discussion of the technical challenges and
155 considerations for the use of animal disease models in safety studies.³ When animal disease
156 models are used in studies to support the clinical usefulness and safety of an ERT product, the
157 IND should include information supporting the usefulness and/or ability of the model(s) to
158 mimic the target disease population and to permit assessment of the safety of the investigational
159 ERT product, taking into account each of the following:
160

- 161 • The similarities and differences between the pathophysiology of the disease in the animal
162 model and the disease in humans
- 163
- 164 • Animal models of disease may demonstrate increased susceptibility to the effects of the
165 investigational ERT versus healthy animals
- 166
- 167 • Possible exacerbation of an existing disease condition or induction of toxicity in response
168 to the investigational ERT
169

³ Morgan, SJ, Elangbam, CS, Berens, S, Janovitz, E, Vitsky, A, Zabka, T, Conour, L, 2013, Use of Animal Models of Human Disease for Nonclinical Safety Assessment of Novel Pharmaceuticals, *Toxicol Pathol*, 41:508-515.

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170 4. *Proof-of-Concept Studies*

171
172 Nonclinical POC studies of ERT in animal disease models are encouraged. These studies can
173 address the objective of establishing biological plausibility before first use in humans. These
174 studies, when designed appropriately, also can be used for assessment of toxicity and to support
175 safety in clinical trials (see section III.B.5). Such studies may also help identify biologically
176 active dose levels and inform a suitable dose-escalation schedule and dosing frequency. The
177 animal model(s) selected for assessment should demonstrate a biological response to the
178 investigational ERT similar to that expected in humans to be informative in support of clinical
179 trials. Pharmacologic activity can be demonstrated through studies that measure tissue substrate
180 levels in animals deficient in (or lacking) the targeted enzyme following treatment with the ERT.
181 In addition, the detection of enzyme-reaction products in the circulation can also serve as
182 evidence of pharmacologic activity.

183
184 Nonclinical in vitro assays intended to assess aspects of the biological activity of an
185 investigational ERT product can provide supporting POC information. In vitro studies can be
186 useful for demonstration of pharmacodynamic activity (e.g., substrate clearance) or the
187 estimation of intracellular half-life of ERTs for lysosomal storage diseases. However, in vitro
188 testing alone is not sufficient to reliably anticipate the outcome of physiological and biologic
189 activity of the product following in vivo administration. Accordingly, the nonclinical testing
190 program should incorporate both in vitro and in vivo approaches to achieve an understanding of
191 the biological plausibility for use of the investigational ERT in the intended patient population.

192
193 Sponsors are encouraged to incorporate safety endpoints in POC studies and should discuss the
194 adequacy of study designs (e.g., number of animals used and comprehensive tissue collection
195 and evaluation) with the review division before study initiation.

196 197 5. *Toxicology Studies*

198
199 An appropriate nonclinical safety assessment should be performed to support the proposed
200 clinical development program. Healthy animals represent the standard test system employed to
201 conduct traditional toxicological studies. For studies to support ERT clinical trials, sponsors can
202 consider study designs that use animal models of disease that incorporate important safety
203 parameters that allow for assessment of the potential toxicity of an investigational ERT. POC
204 studies in relevant animal disease model(s) modified to prospectively assess toxicology
205 endpoints, including microscopic examinations of tissues, should be considered as support for
206 initiation of human clinical trials. The use of animal disease models for toxicity testing may also
207 allow for detection of toxicity caused by the interaction of the drug and the disease in ways that
208 would not be observed in healthy animals. Sponsors should discuss such study designs with the
209 review division before study initiation to obtain agreement on study design.

210
211 The nonclinical safety assessment, whether conducted in healthy animals or animal disease
212 models, should be sufficiently comprehensive to permit identification, characterization, and
213 quantification of potential local and systemic toxicities, their onset (i.e., acute or delayed), the
214 effect of the product dose level on toxicity findings, and the possibility for reversal of any
215 toxicities (if warranted).

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- 216
217 The overall design of the nonclinical studies should support the safety of the proposed clinical
218 trial. Nonclinical toxicology study designs should include the following, as applicable:
219
- 220 • An adequate number of animals per sex that are appropriately randomized to each group.
221 The number of animals needed can vary depending on existing safety concerns for the
222 investigational ERT product, the species, the model, and the delivery system. If safety
223 data are generated from POC studies to support clinical trials, sponsors should consider
224 the use of an adequate number of animals for these studies. Consultation with the review
225 division is recommended for design of these studies before study initiation.
226
 - 227 • Animals with the appropriate age and developmental status as related to the proposed
228 clinical trial population. When a first-in-human trial for an ERT will enroll pediatric
229 patients, toxicity studies that use juvenile animals should be conducted before clinical
230 trial initiation. The major issue is the potential for adverse effects on the developing
231 organ systems in young pediatric patients (e.g., central nervous system, reproductive
232 tract, immune system, and skeletal system). ICH M3(R2) and the guidance for industry
233 *Nonclinical Safety Evaluation of Pediatric Drug Products* provide recommendations for
234 determination of the need for juvenile animal studies. Sponsors can submit the protocol
235 for the juvenile animal toxicology studies to the review division for the division's
236 concurrence before conducting the study. The juvenile animal toxicity studies potentially
237 may be waived when: (1) clinical development is initiated in adult patients; (2) there are
238 no specific safety concerns from studies in adult animals or adult patients; and (3) target
239 organs with identified toxicity concerns are not undergoing development at the time of
240 treatment.
241
 - 242 • Appropriate control groups. A control group should be included in all toxicology studies
243 with ERT products. An example of an appropriate control group includes age-matched
244 animals administered the formulation vehicle only. When it is necessary to co-administer
245 an antihistamine (e.g., diphenhydramine) to control hypersensitivity reactions to the ERT,
246 the study should include a vehicle control group and a vehicle plus antihistamine control
247 group. Justification should be provided for the specific control group(s) selected.
248
 - 249 • Appropriate dose levels. Results obtained from POC studies should guide selection of
250 the target dose levels for both nonclinical safety assessment and for clinical development.
251 ICH M3(R2) and its subsequent questions and answers document provide considerations
252 for selection of high doses for general toxicity studies. In general, the highest doses
253 tested for ERT products should at least achieve some multiple of exposure over the
254 highest proposed clinical-dose regimen. The highest dose level used in nonclinical
255 studies may be restricted because of animal size, tissue volume or size, ROA, or product-
256 manufacturing capacity. Justification, with supporting data, should be provided for the
257 specific dose levels selected.
258
 - 259 • A dosing schedule that reflects the expected clinical exposure, to the extent possible.
260

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

271
272 If the entry criteria define a phenotype that can be expected to rapidly progress to death
273 or substantive irreversible morbidity over the course of 1 year, then repeat-dose
274 toxicology studies in a rodent and a non-rodent species of 1-month dosing duration may
275 be sufficient to initiate clinical trials. Initial dosing in these patients can also be
276 supported by POC studies of appropriate duration in animal disease models, conducted
277 with adequate toxicological assessments. A 3-month toxicity study in one species is
278 needed to support approval of the ERT product for the rapidly progressing disease
279 phenotype. Two species may be needed if the toxicological findings of the 1-month
280 studies in the rodent and the non-rodent are not similar. The 3-month toxicity study or
281 studies should be conducted in parallel with the first-in-human trial.

282
283 If the clinical trial entry criteria define a phenotype that would be expected to have
284 slower disease progression, then toxicology studies in a rodent and a non-rodent species
285 of at least 3 months' duration will be needed to initiate first-in-human trials; this is
286 because, given the chronic nature of these rare diseases, and unmet medical need, chronic
287 dosing would be expected to start with first-in-human exposures.

288
289 In cases where short-term clinical dosing (e.g., less than 1 month) is proposed and
290 considered appropriate, shorter duration toxicology studies may be acceptable as
291 discussed in ICH M3(R2). Longer duration toxicology studies should be completed to
292 support chronic clinical dosing as discussed above.

- 293
294 • An ROA that mimics the intended clinical route as closely as possible. Whenever
295 possible, the delivery device intended for use in the clinical trials should be used to
296 administer the investigational ERT product in the definitive toxicology studies. If it is
297 not possible to replicate the clinical ROA in the animal model, then alternative routes or
298 methods should be proposed and scientifically justified as a part of the nonclinical
299 development plan.
- 300
301 • Safety endpoints that capture potential toxicities. Standard parameters evaluated should
302 include mortality (with cause of death determined, if possible), clinical observations,
303 body weights, physical examinations, food consumption or appetite, water consumption
304 (as applicable), clinical pathology (serum chemistry, hematology, coagulation,
305 urinalysis), organ weights, gross pathology, and histopathology. Additional
306 developmental endpoints may be appropriate when conducting juvenile animal studies.

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- 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

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353 studies, as described in ICH S5(R2) *Detection of Toxicity to Reproduction for Medicinal*
354 *Products & Toxicity to Male Fertility* (refer to ICH M3(R2) regarding the timing of these
355 studies). However, flexibility in timing or requirements for specific studies may be warranted in
356 certain cases with adequate justification. Certain studies can be waived or delayed until after
357 licensure or approval depending on the indicated patient population. Genotoxicity studies are not
358 considered applicable to ERT products and are not recommended. Evaluation of carcinogenic
359 potential generally is not needed to support a marketing application. However, chemically
360 modified ERTs (e.g., a recombinant human enzyme conjugated with a chemical linker) may need
361 an assessment to address the potential for genotoxicity and/or carcinogenicity.

362 8. *Nonclinical Study Reports*

363 A report should be submitted for each in vitro and in vivo nonclinical study intended to
364 demonstrate the safety of an investigational ERT product. Complete reports of pharmacology
365 and POC studies generally are not required for an IND; however, complete study reports should
366 be submitted if the POC studies with safety information are used to support clinical trials. Each
367 complete study report should include, but not be limited to, the following: (1) a prospectively
368 designed protocol and listing of all protocol amendments; (2) a detailed description of the study
369 design (e.g., the test system used, animal species or model used, control and investigational
370 products administered, dose levels, detailed procedures for product administration, and collection
371 of all study protocol parameters); (3) complete data sets for all parameters evaluated, including
372 individual animal data and tabulated/summary data; and (4) analysis and interpretation of the
373 results obtained.

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

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

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