Slowly Progressive, Low-Prevalence Rare Diseases With Substrate Deposition That Result From Single Enzyme Defects: Providing Evidence of Effectiveness for Replacement or Corrective Therapies

Guidance for Industry

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

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Rare Diseases

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Contains Nonbinding Recommendations

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Slowly Progressive, Low-Prevalence Rare Diseases With Substrate Deposition That Result From Single Enzyme Defects: Providing Evidence of Effectiveness for Replacement or Corrective Therapies Guidance for Industry[1]

This guidance represents 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 document provides guidance to sponsors on the evidence necessary to demonstrate the effectiveness of investigational new drugs[2] or new drug uses intended for slowly progressive, low-prevalence rare diseases[3] that are associated with substrate deposition and are caused by single enzyme defects. This guidance applies only to those low-prevalence rare diseases with well-characterized pathophysiology, and in which changes in substrate deposition can be readily measured in relevant tissue or tissues.

This guidance does not apply to products intended for low-prevalence rare diseases with rapidly progressive clinical courses—such conditions can be evaluated by traditional approaches (i.e., using clinical endpoints such as survival, preservation of function, etc.)[4]—or low-prevalence rare

[1] This guidance has been prepared by the Office of New Drugs and the Office of the Center Director in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* or *drug products* include both human drugs and biological drug products regulated by CDER and CBER unless otherwise specified.

[3] For the purpose of this guidance, a disease of low prevalence may be defined as a condition affecting a very small population: for example, approximately a few thousand persons or fewer in the United States. To be eligible for orphan drug designation, a product must be one for a disease or condition that: "(A) affects less than 200,000 persons in the United States, or (B) affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug" (21 U.S.C. 360bb).

[4] Examples of rapidly progressive rare diseases include infantile-onset Pompe disease and infantile-onset lysosomal acid lipase disease.

diseases with previously characterized endpoints predictive of clinical benefit (e.g., normalization of phenylalanine levels for phenylketonuria patients).

FDA encourages sponsors to discuss with the relevant review divisions whether the approach outlined in this guidance applies to their specific drug development programs.

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. DRUG DEVELOPMENT CONSIDERATIONS

There are many reasons that make demonstrating effectiveness extremely challenging for drugs intended to treat slowly progressive, low-prevalence rare diseases that result from defects in a single enzyme. Following are some of those reasons:

- Given the slow progression of the disease, demonstrating clinical stability or clinical improvement may require an extremely long time, even decades in some conditions.

- Developing new disease-specific instruments and endpoints to assess clinical response (e.g., patient-reported outcomes, observer-reported outcomes, new biomarkers) may not be feasible because of the rarity of the disease, geographical distribution of patients, or slow progression of disease manifestations.

- Information on the natural history of the disease may be insufficient to inform the selection of a historical comparator or to inform clinical endpoint selection in future clinical trials.

- In rare circumstances, conducting clinical trials may be impossible because of the extremely low number of patients with a specific disease or with a clinical manifestation of interest for a given disease.

- When more than one potential therapy is investigated concomitantly, the pool of potential patients is further reduced.

Sponsors should take the following into consideration when developing a rational approach to drug development:

- A genetic defect affecting a single enzyme can result in either the absence of, or a low level of, enzyme activity, with subsequent accumulation of substrates that may be toxic to various tissues. Residual enzyme activity often inversely correlates with substrate accumulation.

- An increase in enzyme activity resulting from the administration of an exogenous enzyme product, by reducing the amount of substrate accumulated and/or by slowing substrate accumulation, may alter the rate of disease progression or, over time, shift the disease phenotype to a milder one.

- The amount of enzyme activity necessary to prevent or reduce abnormal substrate accumulation can vary considerably among tissues.

- Replacement enzymes may penetrate different tissues and subcellular compartments to a different extent, which may result in differences in response to treatment in various tissues.

- Evidence of activity requires not only evidence that the drug reaches the target organ and subcellular compartment of interest but also a demonstration that the drug reduces substrate accumulation.

- Some biomarkers (other than substrates) are very closely linked to the underlying pathophysiology of the disease (e.g., they can be directly linked to a missing metabolite on a critical metabolic pathway). Sponsors can use changes in such biomarker levels during drug development for dose selection or patient selection, and these changes can serve as an early demonstration of drug activity, but they are not a replacement for demonstration of reduction in substrate deposition in the tissues of interest in clinical trials.

Sponsors can apply several strategies for treating slowly progressive, low-prevalence rare diseases that result from defects in a single enzyme, including the following:

- Administering a fully functional exogenous enzyme that reaches the organ or organs of interest. This is commonly referred to as enzyme replacement therapy.

- Ameliorating the enzyme defect by using a pharmacologic chaperone that binds to the mutant enzyme, inducing proper folding, ensuring correct intracellular trafficking, and preventing premature enzyme degradation.

- Reducing the rate of synthesis of substrates.

- Diverting an accumulating substrate to an alternative metabolic pathway.

- Introducing the wild type gene into somatic cells using viral vectors.

III. TYPE AND QUANTITY OF EVIDENCE NECESSARY TO SUPPORT EFFECTIVENESS FOR REPLACEMENT OR CORRECTIVE THERAPIES

As discussed in section II., for certain slowly progressive, low-prevalence rare diseases, sponsors can pursue various treatment strategies to halt or slow the abnormal accumulation of substrate in tissues. When the pathophysiology of a disease is well understood and the mechanism of action of the drug/biologic is well characterized, specific drug-induced substrate reduction in relevant tissue or tissues can have a reasonable likelihood of predicting clinical effectiveness. In such a case, a clear demonstration in clinical trial or trials that an exogenously administered enzyme or drug results in substrate reduction (i.e., it reaches the tissue of interest) can serve as the basis for accelerated approval.

For drugs granted accelerated approval, postmarketing confirmatory trials are required to verify and describe clinical benefit by evaluating one or more clinical endpoints.[5] In some instances, further evaluating (e.g., longer duration of treatment and progressive reduction or resolution of substrate deposition) the same histological endpoint that was used to support accelerated approval in the same or similar population could provide persuasive evidence of clinical benefit and could support full approval.

The following sections describe what FDA considers substantial evidence of effectiveness to support accelerated approval for an investigational new drug replacement or corrective therapy or new drug use intended to treat a slowly progressive, low-prevalence rare disease with substrate deposition that is caused by a single enzyme defect.

In the absence of a way to directly characterize the clinical response to the drug of interest (i.e., how a patient feels, functions, or survives), the nonclinical and, particularly, the clinical pharmacology components of the drug development program become the main source of data that 1) support a safe dose that can be used to initiate human studies and 2) inform dose exploration, which is essential to final dose selection for clinical trials.

The following sections emphasize how sponsors can use nonclinical and clinical pharmacology information, along with additional sources of information (e.g., in vitro data), to inform dose selection for clinical trials meant to lead to marketing approval.

A. Animal Toxicology/Pharmacology and Animal Models of Disease Activity — Major Considerations

This section highlights some aspects of the nonclinical program that could inform drug development in slowly progressive, low-prevalence rare diseases.

[5] Section 506(c)(2)(A) of the Federal Food, Drug, and Cosmetic Act. See also 21 CFR part 314, subpart H and 21 CFR part 601, subpart E.

- Evaluation of the toxicological profile in animals is important for all drug development programs.[6]

- Disease-specific animal models are desirable for drug development in rare diseases. Conserving metabolic pathways and essential intermediary components between animal species and humans (e.g., ligands, cognate receptors, critical enzyme domains) can generate a wealth of relevant pharmacokinetic/pharmacodynamic and proof-of-concept information (e.g., animal disease improvement, survival) that can guide testing of investigational drug products in humans.

- Some animal models of single-gene human storage disorders display phenotypes that mimic to a large extent the clinical manifestations and overall course of the human disease (e.g., tripeptidyl peptidase null dachshund dog model for tripeptidyl peptidase deficiency) and offer opportunities for evaluating the effect of human enzymes in situations in which there is significant structural and functional conservation of the missing enzyme across species. Animal models can provide opportunities for histological studies and demonstrate penetrance of a specific drug in the tissue of interest, including reaching specific subcellular compartments (e.g., lysosomes). Moreover, such animal models can provide evidence of enzyme activity by demonstrating the reduction or disappearance of disease-specific substrates.

- Although not all animal models mimic the human phenotype, FDA encourages sponsors to develop relevant models, given the potential benefit for future drug development.

- Demonstration of benefit in animal models for a specific drug product may support initiation of clinical studies in pediatric patients by meeting 21 CFR subpart D requirements for prospect of direct benefit.[7]

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[6] See the draft guidance for industry *Investigational Enzyme Replacement Therapy Products: Nonclinical Assessment* (October 2019). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents. See also 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). For recommendations on the substance and scope of nonclinical information needed to support clinical trials for cell therapy and gene therapy products, see the guidance for industry *Preclinical Assessment of Investigational Cellular and Gene Therapy Products* (November 2013). 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/RegulatoryInformation/Guidances/default.htm. For complex biological products (e.g., gene therapy), alternative approaches may be needed for animal studies as well as for demonstration of effectiveness. FDA encourages sponsors to discuss their proposals with the appropriate CBER product office. FDA also 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 as a potential replacement to an animal test method.

[7] 21 CFR 50.52.

B. First-in-Human Dosing and Dose Selection — Key Considerations

In selecting specific doses for slowly progressive, low-prevalence rare diseases that are caused by a defect in a single enzyme, sponsors should consider the following:

- Because efficient patient utilization remains a critical component of any rare disease clinical program, sponsors should use any available sources of information (e.g., publications, experience with similar compounds, experience in related patient populations) during dose selection.

- Testing enzyme replacement therapies in healthy subjects may not be appropriate because of the potential risk of inducing an immune response to the investigational drug product and cross-reactivity of the elicited antibodies with the endogenous protein and the risk of inducing a deficient state in such subjects.

- Using nonhuman data obtained in animal models of disease and in vitro data may be, in some cases, the only way to estimate a starting human dose that sponsors hypothesize will provide clinical benefit.[8] Sponsors can obtain additional dosing information from predictive models based on current understanding of in vitro enzyme kinetics (including characterizing the enzyme kinetics in relevant cell lines) and allometric scaling.

- Animal toxicology data may inform a safe starting human dose.[9]

- Sponsors may be able to use effective dose finding in an informative animal model of human disease with the knowledge of blood levels and tissue levels to identify an initial estimate of a human equivalent dose with appropriate extrapolation (e.g., allometric scaling). Such data can also provide initial estimates of dose-response relationships.

- The selection of the dose and regimen for clinical trials may be optimized based on available clinical and nonclinical observations or mechanistic/model-based approaches that consider dose- or concentration-response relationships, factors affecting pharmacokinetics (e.g., body weight, organ function), and disease characteristics (e.g., baseline deficit of the enzyme/enzyme function, severity).

- In clinical trials, sponsors should consider evaluating two or more dose levels. Although a parallel design is considered the best approach for dose exploration, this approach may not be feasible for some diseases or patient populations. Dose evaluation within subjects may provide an alternative approach. For within-subject dose exploration, sponsors should take into consideration carryover effects from the previous dose, and the treatment duration should be sufficiently long to allow adequate evaluation of the response at each dose level.

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[8] See the guidance for industry *Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers* (July 2005).

[9] See ICH M3(R2), ICH M3(R2)—*Questions and Answers*, and the guidance for industry *Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers*.

- Sponsors should consult with the Agency as early as possible to discuss important issues such as model-based strategies, dose selection, study design, and endpoint analyses.

C. Providing Evidence of Substrate Reduction

Sponsors should discuss with the Agency any plan to generate evidence of substrate reduction in clinical trials. Such evidence should be generated in tissues in which changes in substrate deposition can be readily measured, and the relevance of changes in these tissues to the overall disease process must be well understood and clearly justified. Sponsors should also address how the treatment effect size relates to the variability in the test measure. To this end, sponsors should consider the following:

- If substrate levels are heterogeneous in the tissue of interest, efforts to produce a representative measurement of the substrate in the tissue may improve the ability to detect a treatment effect. For example, sponsors may obtain multiple specimens from the subject to produce an average result at a given time point as a way to address heterogeneity in the tissue.

- Sponsors should perform complete analytical validation for all assays used to measure the substrate levels. This validation should include acceptance criteria for analytical performance characteristics. FDA recommends centralized testing of substrate level endpoints. If local assays are necessary for the purposes of conducting the trial (e.g., for adaptive dosing), sponsors should also obtain specimens for centralized testing. If centralized testing is not feasible, sponsors should perform cross-validation of the assays conducted at local laboratories.

- Preanalytical sample handling can significantly influence assay performance. Sponsors should establish standard operating procedures for the collection, storage, and shipment of biospecimens that should be followed at each trial site with deviations recorded. Preanalytic reagents and instrumentation should also be validated.

D. Other Considerations

The following considerations are intended to inform the assessments of efficacy or safety in clinical trials:

- Because most rare diseases are pediatric diseases or have onset of manifestations in childhood, pediatric studies will be a critical part of drug development. However, treatment in pediatric patients cannot proceed without addressing ethical considerations for conducting investigations in vulnerable populations. Unless the risks of an investigational drug are no more than a minor increase over minimal risk (21 CFR 50.53), the administration of an investigational drug in children must offer a prospect of direct clinical benefit to individually enrolled patients, the risk must be justified by the anticipated benefit, and the anticipated risk-benefit profile must be at least as favorable as

that presented by accepted alternative treatments (21 CFR 50.52). Additionally, sponsors must make adequate provisions to obtain the permission of the parents and the assent of the child as per 21 CFR 50.55.[10]

- Sponsors should perform genetic testing and provide genotypes for the defect or defects of interest in all clinical trial subjects.

- For therapeutic protein products, sponsors should evaluate immunogenicity in all trial subjects using an analytically validated assay. Also, sponsors should determine cross-reactive immunologic material status in all clinical trial subjects as part of the immunogenicity assessment. For this, FDA recommends that sponsors collect and store blood (or other relevant tissue) samples at baseline before initiating treatment. Refer to the appropriate guidances regarding assessment of immunogenicity.[11]

- Sponsors should consult with FDA regarding additional clinical outcome data that could be systematically collected to assess clinical benefits in individual subjects.

[10] 21 CFR 50.52.

[11] See the guidance for industry *Immunogenicity Assessment for Therapeutic Protein Products* (August 2014) and the draft guidance for industry *Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products* (April 2016). When final, this guidance will represent the FDA's current thinking on this topic.

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Platt FM and Butters TD, 1998, New Therapeutic Prospects for the Glycosphingolipid Lysosomal Storage Diseases, Biochem Pharmacol, 56(4):421–430.

Guidances for industry

Draft guidance for industry *Rare Diseases: Common Issues in Drug Development* (February 2019)[1]

Guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics* (May 2014)

Guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998)

Prescribing information

Cholbam (cholic acid) available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205750s000lbl.pdf.

Fabrazyme (agalsidase beta) available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103979s5135lbl.pdf.

Kanuma (sebelipase alfa) available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125561s000lbl.pdf.

Myozyme (alglucosidase alfa) available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125141s219lbl.pdf.

[1] When final, this guidance will represent the FDA's current thinking on this topic.