Inborn Errors of Metabolism That Use Dietary Management: Considerations for Optimizing and Standardizing Diet in Clinical Trials for Drug Product Development

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Division of Rare Diseases and Medical Genetics, Dina Zand at 240-402-2538, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
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Inborn Errors of Metabolism That Use Dietary Management: Considerations for Optimizing and Standardizing Diet in Clinical Trials for Drug Product Development Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

I. INTRODUCTION

This guidance describes the Food and Drug Administration's (FDA's) current recommendations for optimizing and standardizing dietary management in clinical trials for drug products intended to treat inborn errors of metabolism when dietary management is important for metabolic control.[2] Optimizing and standardizing dietary management in patients diagnosed with inborn errors of metabolism before they enter clinical trials and during clinical trials reduces an important source of bias and variability, improves interpretability, and may allow for smaller and more efficient clinical trials.

This guidance does not address scenarios in which dietary optimization and standardization may be infeasible (e.g., diseases with prominent neuropsychiatric symptoms). For those programs, bias from differential dietary management can best be addressed with randomization and blinding. This guidance also does not address general issues of statistical analysis or clinical trial design. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* (September 1998) and *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001), respectively.[3]

This guidance revises the draft guidance of the same name issued on July 24, 2018. This revision clarifies that:

[1] This guidance has been prepared by the Division of Rare Diseases and Medical Genetics 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 this guidance, the term *drug products* includes both human drugs and biological drug products regulated by CDER and CBER unless otherwise specified.

[3] We update guidances periodically. 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.

- Drug products should be studied in conjunction with dietary management for conditions where dietary management is the current standard of clinical care.

- The most informative design is a randomized, double-blind clinical trial that includes a concurrent control group (approved drug or placebo).

- Metabolic control may be evaluated by biochemical analytes and clinical assessment as substantiated by current clinical standards of care.

- Dietary optimization should be based on dietary standards for the relevant population and account for the severity of the patient's metabolic defect and the patient's age, growth, and general health status.

- Baseline dietary management standards among patients from different countries should be explained in the protocol.

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

Dietary management is an important treatment modality and standard of care for several inborn errors of metabolism where specific enzymatic defects result in reduced or absent metabolism of a variety of dietary components, with subsequent accumulation of toxic metabolites and organ damage. Dietary management involves restricting particular food components, for example:

- Restricting protein for patients diagnosed with urea cycle disorders or organic acidemias

- Limiting food containing certain fats in patients diagnosed with some fatty acid oxidation defects

- Limiting carbohydrates in patients diagnosed with certain primary mitochondrial diseases

- Removing dietary galactose in patients diagnosed with classical galactosemia

- Limiting phenylalanine in patients diagnosed with phenylketonuria

In some inborn errors of metabolism, dietary management includes supplementation with special formulas that lack specific components (e.g., amino acids or galactose) and the recommendation to ingest vitamins or cofactors that are important and unique to the patient's metabolic pathway deficiency.

The goal of dietary modification is to improve or restore biochemical and physiologic homeostasis by restricting the dietary precursors that generate intermediary products of metabolism that may accumulate and lead to toxicity in specific diseases.

Drug products (e.g., enzyme replacement therapy, enzyme substitution therapy) should be studied in conjunction with dietary management for conditions that use dietary management as part of clinical care. Clinical trials for these drugs typically include measurements of metabolite concentrations (primarily in serum and urine) as endpoints, which are the same assessments used to inform dietary changes and to determine whether dietary management has been optimized. Consequently, dietary changes during these trials can affect efficacy results and pose significant interpretability challenges, particularly when the clinical trial does not anticipate or appropriately account for the confounding effect of diet in the design and analyses of trial results. This confounding can add to the existing challenges in designing and conducting successful clinical trials in rare diseases, such as the limited availability of patients (thus, the small size of clinical trials), the heterogeneity of clinical phenotypes, the challenges with selecting appropriate efficacy endpoints, and the lack of precision of dietary assessments. Inadequate dietary management or insufficient documentation of dietary changes during a trial can make interpretation of trial results particularly difficult when the treatment effect of the new drug product is not large.

III. RECOMMENDATIONS

A. Optimizing, Standardizing, and Maintaining Diet Stability in Clinical Trials

Sponsors should consider the following recommendations for optimizing, standardizing, and maintaining the diets of patients before they enter clinical trials:

- When optimizing a patient's dietary management before trial entry, sponsors should take into account the specific condition that is being treated; the severity of each patient's metabolic defect; the patient's age, growth, and general health status; the duration needed to assess whether the patient's dietary management is appropriate and optimized for the patient's individual medical needs; and the complexity of, and the patient's/family's ability to understand and comply with, the prescribed diet.

- Sponsors should assess and systematically document patient adherence to the dietary plan during the trial. Protocols should include standard measures to verify adherence to the dietary plan (e.g., periodic testing for specific metabolites over time based upon age-related standards, appropriate growth assessments, etc.).

- Sponsors should evaluate the patient's ability and likelihood of complying with the recommended diet to ensure that patients with a high likelihood of maintaining a stable diet during the trial are enrolled.

- The duration of the run-in period for diet optimization should be justified.

- Given the global nature of rare disease trials, sponsors should have an awareness of and clearly state the differences in standards in baseline dietary management among patients from different countries.

Sponsors should consider the following dietary recommendations for subjects who are participating in the treatment phase of the clinical trial:

- During the trial, patients should maintain a stable diet, and any changes should be documented in a diary and accompanied by the reasons for the changes.

- Sponsors should follow the same principles of dietary management across clinical sites according to protocol-defined and allowed dietary modifications. For consistency, the trial protocol should define clearly both the dietary goals and the dietary management, including use of standardized household measurements and scale-measuring devices for estimating volume and weight of food, whenever possible.

- Protocols should include precise definitions of diet stability during the trial, including magnitude of allowed deviations generally anticipated in the prescribed diet, such as ± 5% or other change in total daily protein. This definition should be scientifically justified and supported by evidence that a certain dietary deviation will not affect the clinical and laboratory outcomes assessed in the trial.

- Patients should enter the treatment phase of the trial during a period of stable metabolic control as evaluated by appropriate biochemical analytes (e.g., ammonia, plasma amino acids, urine organic acids, plasma acylcarnitines, total and free carnitine) and clinical assessments. Sponsors should document baseline dietary information (total daily protein, lipid, carbohydrate, and total daily caloric intake) over an appropriate time period (e.g., 3 days) at enrollment.

B. Procedures and Intercurrent Illnesses

Patients with inborn errors of metabolism often require increased caloric intake for procedures or assessments requiring sedation that can include dental care, adenoidectomy or gastrostomy tube placement, in addition to intercurrent illnesses that may precipitate a change in metabolic status (e.g., metabolic decompensation with need for dietary and/or pharmacologic changes). Ideally, sponsors should anticipate and address elective surgeries and procedures before enrolling patients in clinical trials. However, protocols also should specify a standardized approach to dietary management for unanticipated intercurrent procedures, illnesses, and metabolic events that may occur during the trial. Adherence to this approach should be documented systematically and addressed in the statistical analysis plan, including how these intercurrent events will impact the efficacy and safety assessments and clinical interpretation of data.

C. Clinical Trial Design

Sponsors should consider the following recommendations for clinical trial design when an investigational drug is compared with an approved drug or placebo as add-on to dietary management. General considerations include the following:

- The most informative design is a randomized, double-blind clinical trial that includes a concurrent control group (approved drug or placebo). Dietary management should be consistent across all trial arms such that regardless of treatment arm, all patients should be receiving optimized standard of care, including dietary management.

- Sponsors can consider different types of controlled, randomized clinical trial designs (e.g., crossover, randomized withdrawal, delayed start). An active-controlled noninferiority design is one possible approach if there is an already approved therapy and it is possible to justify a noninferiority margin.[4] Sponsors should discuss the specific trial designs with FDA for concurrence before initiating the trial.

- Changes in dietary management during a trial can introduce variability, reducing the potential to find benefit for an effective treatment. Dietary changes made to account for growth or disease exacerbation should be prespecified and clearly documented.

- Sponsors should discuss with FDA any performance-based or clinical outcome assessment tools for endpoints intended to establish substantial evidence of effectiveness, including those that may be influenced by dietary changes, before implementing those assessments in a trial(s).

To allow for unbiased comparative efficacy assessments when trials involve dietary management, the use of a concurrent blinded control arm is an essential aspect to the clinical trial design. Comparisons to a nonconcurrent, historical control group have important limitations for the following reasons:

- Standards for dietary management can change over time. An optimized diet for a historical control group may differ from an optimized diet for a concurrent control group or a treatment group in a given trial. This difference can introduce bias in comparisons, as differences in dietary practice can affect the results of the clinical outcomes.

- Differences in the frequency and type of dietary instructions can lead to differences in dietary management and compliance between treatment groups, which can bias efficacy analyses.

- Differences in patient documentation of diet can limit the ability to compare dietary management and compliance between treatment groups.

[4] See the guidance for industry *Non-Inferiority Clinical Trials to Establish Effectiveness* (November 2016).

- Differences in patient baseline characteristics between the historical control group and the treatment group, some of which may be unmeasured, can limit the ability to conduct reliable comparisons.

- The standards of disease management, including management of concurrent or related conditions, change over time. Changes in disease management compared with a historical control group can also introduce bias.

- The types and performance characteristics of laboratory assays used to measure metabolic biomarkers/endpoints among the groups can change over time. It is important that sponsors account for these changes when using these assays to evaluate biochemical parameters of metabolic control and to assess dietary compliance or dietary optimization and response to treatment.

D. Challenges and Limitations of Diet Assessments

Although assessments of dietary intake have been used to document dietary practices and to verify the patient's diet adherence, available tools that measure dietary components have limitations. Sponsors should consider the following:

- Dietary questionnaires use crude measures of portion size, frequency of consumption, and broad food groupings and are only a general estimate of dietary intake. Thus, day-to-day and week-to-week variation in diets could lead to a range of estimates of long-term dietary intake.[5]

- Food diaries (e.g., 3-day diet) are commonly used in the clinical management of patients with inborn errors of metabolism. The inherent variability of patient/family recall in a food diary may introduce imprecision into a clinical trial and should be avoided. Using standardized dietary forms (written or electronic) designed or vetted by metabolic dietitians and physicians can greatly facilitate dietary documentation in a clinical trial and is strongly encouraged.

- Sponsors should encourage families and patients to document their diet frequently during the trial to support the routine documentation obtained during the 3 days before clinical site visits.

[5] Greenwood DC, MS Gilthorpe, and JE Cade, 2006, The Impact of Imprecisely Measured Covariates on Estimating Gene-Environment Interactions, BMC Med Res Methodol, 6:21.