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DRAFT GUIDANCE

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

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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]

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I. INTRODUCTION

This guidance describes the Food and Drug Administration's (FDA's) current recommendations regarding how to optimize and standardize dietary management in clinical trials for the development of drugs that treat inborn errors of metabolism (IEM) for which dietary management is a key component of patients' metabolic control.[2] Optimizing dietary management in these patients before entry into and during clinical trials is essential to providing an accurate evaluation of the efficacy of new drug products.

This guidance does not contain discussion of the 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* and *E10 Choice of Control Group and Related Issues in Clinical Trials*, respectively.[3]

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.

[1] This guidance has been prepared by the Division of Gastroenterology and Inborn Errors Products 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. 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.

II. BACKGROUND

Dietary management is the main treatment modality for several inborn errors of the intermediary metabolism in which mutations in specific enzymes result in an inability to break down a variety of dietary components, with subsequent accumulation of toxic metabolites and organ damage. Diet modification is standard of care for the treatment of these conditions. The goal of diet modification is to restore biochemical and physiologic homeostasis by restricting the dietary precursors that generate toxic metabolites.

Drug products have been developed to complement diet and further improve metabolic control in IEMs such as phenylketonuria, organic acidemias, and urea cycle defects. Development programs for such drug products utilize the same assessments used to inform dietary changes and to determine whether dietary management has been optimized. These assessments are measurements of concentrations of metabolites primarily in serum and urine. Consequently, in clinical trials intended to support a marketing application for a new drug product, dietary changes can affect efficacy results and pose significant interpretability challenges, particularly when the clinical trial design did not anticipate or appropriately account for the confounding effect of diet. This confounding effect can add to the existing challenges in designing and conducting successful clinical trials, which include the limited availability of patients (and, thus, the small size of clinical trials), the heterogeneity of clinical phenotypes, and the lack of precision of dietary assessments. A trial's inadequate dietary management can make interpretation of results particularly difficult when the average treatment effect of the new drug product is relatively modest.

III. RECOMMENDATIONS

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

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

- Patients should have optimized and stable diets, and the patients should follow the same principles of dietary management across clinical sites during the trial. To ensure consistency, the trial protocol should define clearly both the dietary goals and management.

- Sponsors should select the duration of the pretrial period for optimizing and stabilizing a patient's diet based on the specific condition that is being treated, the severity of the metabolic defect, the patient's age, and the complexity of the dietary management.

- Patients should enter the trial during a period of metabolic control as demonstrated by appropriate biochemical analytes (e.g., ammonia, plasma amino acids, urine organic acids, plasma acylcarnitines, total and free carnitine). Baseline dietary information (total daily protein, lipid, carbohydrate, and total daily caloric intake) should be documented

over an appropriate time period (e.g., 3 days) at enrollment even if metabolic stability has been shown.

B. Planned Procedures

Surgeries (e.g., adenoidectomy) and other procedures (e.g., gastrostomy tube placement) are common in patients with IEMs and often require a concomitant increase in caloric intake. As any change in dietary intake will affect the interpretability of clinical trial data, these procedures should be completed before a patient enrolls and followed by a period of dietary and metabolic stability.

C. Clinical Trial Design

Sponsors should consider the following recommendations for clinical trial design.

- General considerations include the following:
  - The most informative design is a randomized, double-blind clinical trial that includes a concurrent control: either an approved drug product for the same indication or, in the absence of an approved drug, a placebo.
  - Sponsors can consider different types of controlled, randomized clinical trial designs (e.g., crossover, randomized withdrawal, delayed start). With a well-defined effect that can be used to develop a noninferiority margin, an active controlled trial design can be used depending on the specific characteristics of the disease of interest and the availability of endpoints.[4] Sponsors should discuss the specific trial designs with the FDA for concurrence before initiating the trial.
  - FDA discourages nonrandomized trial designs in which a cohort of patients receiving only dietary management is switched to dietary management plus drug product treatment (i.e., switchover trials). Without a concurrent control arm and blinding, switchover designs are unlikely to produce interpretable results.
- Considerations for optimizing diet include the following:
  - To ensure selection of a compliant group of patients, FDA recommends a run-in period during which patients' and caregivers' commitment to following the trial's procedures and, in particular, dietary instructions is assessed.
  - Clinical trial protocols should include a clear and detailed description of the dietary management plan. Patients' adherence to the dietary plan should be assessed systematically. Protocols should include standard measures to verify adherence to diet (e.g., periodic testing for specific metabolites, appropriate growth assessments).

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

- Protocols should specify frequency of visits and include guidelines for dietary management during intercurrent illnesses or disease exacerbations.

- Statistical analysis plans should provide a detailed strategy to assess the role of diet adherence in the estimation of the drug product effect, including sensitivity analyses.

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:

- Food frequency questionnaires use crude measures of portion size, frequency of consumption, and broad food groupings and are an 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 are commonly used by metabolic nutritionists for the clinical management of IEM patients. The inherent variability of patient recall in the completion of a food diary may introduce imprecision into a clinical trial and should be accounted for in the trial design and efficacy analyses.

- Given the importance of accurately collecting good quality dietary information to ensure the interpretability of efficacy data, the sponsor should discuss selection of a specific measure with the FDA before implementing the measure in the clinical trial(s).

E. Use of Historical Controls

Efficacy comparisons of historical controls with an investigational drug product group are unlikely to be informative for the following reasons:

- Changes in standards for dietary management over time. An optimized diet for a historical control group may differ from the optimized diet for a concurrent control or an investigational drug product group.

- Differences in the frequency and type of dietary instructions given to patients before and during the trial.

- Differences in the documentation of dietary management procedures implemented during the trial.

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

- Differences in patient and clinical trial characteristics between the source of the historical controls and the investigational drug product group under consideration.

- Differences between contemporary standards for investigator training and that of the time when historical control data were collected.

- Differences in the types and performance characteristics of assays used to measure metabolic biomarkers/endpoints.

- Open-label trials, in and of themselves, are subject to potential bias.