Guidance for Industry Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs

DRAFT GUIDANCE

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

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Guidance For Industry[1]

Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to assist manufacturers of exocrine pancreatic insufficiency drug products in preparing and submitting new drug applications (NDAs). This draft guidance is being issued concurrently with a notice in the *Federal Register* announcing that all orally administered pancreatic enzyme products (PEPs) are new drugs which will be approved for prescription use only, and explaining the conditions for continued marketing of these drug products.

FDA's guidance documents, including this guidance, 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

Pancreatic enzyme preparations of porcine or bovine origin have been available in the United States for the treatment of exocrine pancreatic insufficiency (EPI) in children and adults with cystic fibrosis and chronic pancreatitis since before the enactment of the Federal Food, Drug, and Cosmetic Act of 1938 (the Act). Under the Act, beginning in 1938, new drugs were required to

[1] This guidance has been prepared by the Division of Gastrointestinal and Coagulation Drug Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA).

be the subject of approved NDAs. With the exception of one PEP approved in 1996, PEPs have been marketed without NDAs.

There are approximately 30,000 children and adult patients with cystic fibrosis in the United States. Pediatric patients affected with cystic fibrosis (CF) and patients with chronic pancreatitis (CP) who have significant reduction of pancreatic function are unable to digest fats, proteins, and carbohydrates. As a consequence, the absorption of these nutrients is impaired, with the resultant malnutrition and a host of secondary complications, including retarded growth and development, impaired immune response, infections, and bleeding tendencies, among others.

PEPs contain the ingredients pancreatin and pancrelipase, both of which contain the enzymes lipase, protease, and amylase. These enzymes break down fats (lipase), proteins (protease), and complex carbohydrates (amylase) into elementary units of small size that can traverse the intestinal mucosa, incorporate into the blood stream, and work as sources of energy and building blocks of tissues.

In the *Federal Register* of November 8, 1985 (50 FR 46594), FDA published a notice of proposed rulemaking to establish a monograph for over-the-counter (OTC) exocrine pancreatic insufficiency (EPI) drug products. The Agency accepted the recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products (the Panel) that EPI drug products be considered safe (generally recognized as safe, GRAS)[2] and effective (generally recognized as effective, GRAE)[3] and not misbranded. Interested persons were invited to submit new data, written comments, objections, or requests for an oral hearing on the proposed rulemaking. Based on the information received, the FDA reconsidered the approach in the November 8, 1985, proposed rulemaking and concluded that (1) an OTC monograph would not be sufficient to adequately regulate these drug products, (2) preclearance of each product to standardize enzyme bioactivity would be necessary, and (3) continuous physician monitoring of patients would also be necessary. It was the Agency's intent that such products be available by prescription only. In the *Federal Register* of July 15, 1991 (56 FR 32282), FDA proposed a regulation that would declare that OTC drug products used to treat EPI are not GRAE and GRAS and are misbranded. The final rule published on April 24, 1995 (60 FR 20162).

In the proposed and final rules, the FDA discussed its review of the scientific data that provide the basis for the FDA's decision to require approval of PEPs through the new drug approval (NDA) process under section 505 of the Act.

At this time, FDA expects to receive only NDAs, including section 505(b)(2) applications, for these products.[4] For the reasons described below, the Agency has determined that pancreatic

[2] GRAS, see 21 CFR 330.1.

[3] GRAE, see also 21 CFR 330.1.

[4] If the products vary by active ingredient (e.g., product 1: amylase and lipase; product 2: amylase and protease), then a separate application should be submitted. If the products vary only by potency ratios of the same active ingredients (e.g., product 1: amylase, 15,000 amylase units, lipase, 1,200 lipase units, and protease, 30,000 protease units, and product 2: amylase, 15,000 amylase units, lipase, 1,500 lipase units, and protease, 35,000 protease units),

extract drug products currently are not likely to be appropriate subjects for abbreviated new drug applications (ANDAs).

For a pancrelipase or pancreatin product to be approved as an ANDA, the proposed drug product would have to be shown to contain the same active ingredient(s) as an approved reference listed drug. Because of the complexity of pancreatic extract products, it is unlikely that currently available physiochemical and biological analytical tools would be able to demonstrate that the active ingredients in pancreatic extract products from two different manufacturers are the same. Therefore, the Agency has concluded that manufacturers currently are unlikely to obtain approval of pancreatic extract products under section 505(j) of the act.

Manufacturers interested in submitting ANDAs for pancreatic extract products are strongly advised to contact the Office of Generic Drugs (HFD-600) (Center for Drug Evaluation and Research, Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855) to discuss the feasibility of such an application.

III. CHEMISTRY, MANUFACTURING, AND CONTROLS SECTION OF THE APPLICATION

An NDA application must meet the requirements described in 21 CFR Part 314. Applicants should consult FDA's *Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances*, *Submitting Documentation for the Manufacture of and Controls for Drug Products*, and other related CDER guidances.[5] Applicants should also consult relevant International Conference on Harmonisation (ICH) guidance documents (e.g., Q1A, Q2A, Q2B, Q3C, Q5A, Q5C, and Q6B). Information unique to PEPs that should be provided in NDAs is described below.

A. Drug Substance

For the starting material used in the manufacturing process, information on animal species, tissue types, and countries of origin should be provided. Animals used should have been raised with the intent for use as human food. When ruminant tissues are used, they should not be derived from cattle born, raised, or slaughtered in BSE (bovine spongiform encephalopathy) countries (see 9 CFR 94.18).

The manufacturing (extraction and purification) process should be validated for its capability to remove and/or inactivate viral agents as recommended in ICH *Q5A*.

The drug substance should be fully characterized (based on ICH Q6B) using appropriate chemical, physical, and biological testing. Batch-to-batch consistency with respect to chemical

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then separate NDAs need not be submitted. Different strengths or concentrations can be submitted in the same NDA.

[5] Agency guidances are available on the Internet at http://www.fda.gov/cder/guidance/index.htm.

identity, biological activity of different classes of enzymes including specific activity, and purity level should be demonstrated. Identity may be demonstrated by fingerprint analysis, using (but not limited to) the following methods:

- Chromatography (e.g., ion-exchange or reversed phase high-pressure liquid chromotography (HPLC))
- SDS-PAGE (sodium dodecyl sulfate-polyacrylamide gel electrophoresis)
- Isoelectric focusing (IEF)

Similar methods can also be used to determine chemical purity. New analytical technology should be used when appropriate.

Specifications for the drug substance should include tests for identity, biological activity of different classes of enzymes, purity, and other relevant attributes. Appropriate acceptance factors (e.g., limits and ranges) should be established and justified.

B. Drug Product

Specifications for the drug product should include tests for identity, biological activity of different classes of enzymes, degradants, dissolution, and other relevant attributes. Appropriate acceptance factors should be established and justified. When a novel or non-novel but non-compendial excipient is included in the formulation of the drug product, manufacturing and control information on the excipient should be provided. Refer to related sections in ICH Q6B.

C. Stability

Due to the inherent lability that has been observed with PEPs, stability data through 12 months at the recommended storage temperature as well as 3 months of accelerated stability data should be provided.

Additional stability data can be submitted as an amendment during the review process, and an expiration date will be determined based on the review of the stability data in the NDA.

Primary stability data should be generated according to the guidance developed in ICH Q1A and Q5C. Primary stability studies should be performed with batches that are formulated to be released at 100 percent of the label-claimed potency. The proposed shelf life should not depend on the existence of a stability overage.

Existing stability data not obtained under ICH conditions can be submitted as supporting data.

D. Overages

The finished product should be formulated to be released at 100 percent of the label-claimed potency to reflect accurate labeling, to reduce batch-to-batch variability in potency, and to reduce the amount of accumulated degradants in the product. As a result, patients will at no time receive a much higher or lower dose than intended, a possible safety concern.

E. Dissolution Method

For novel dosage forms, an appropriate in vitro release test method should be developed. The dissolution method (or an appropriate modification of it) provided in the United States Pharmacopeia (USP) can be used.

IV. NONCLINICAL PHARMACOLOGY AND TOXICOLOGY SECTION

A. Toxicology

No toxicology studies are needed if excipients are classified as GRAS for oral administration.[6] Safety should be established through toxicology studies of new excipient(s) of the drug product which are not included under GRAS or not previously approved for the same route of administration, amount, or therapeutic use. For new excipients without previous clinical data, clinical trials of the drug product containing the new excipients should also be performed. If the new excipients are included under GRAS but are present in quantities in excess of the allowed levels, their safety should be established at the higher levels through toxicological studies of the excipients or the drug product containing the higher levels of the excipients. To determine their safety, the toxicology program for new excipients or for excipients with higher levels than listed for GRAS should supply data from long-term studies in a rodent and a nonrodent mammalian species plus standard reproductive toxicity and genotoxicity information (see Steinberg et al., *A New Approach to the Safety Assessment of Pharmaceutical Excipients, Regulatory Toxicology and Pharmcology*, 24, 149-154, 1996).[7] Information from published reports of toxicology studies should also be included in the NDA.

B. Pharmacology

Because of the extensive use of the marketed PEP products, no new pharmacology studies are necessary. FDA recommends applicants to summarize the published literature about the pharmacology of PEPs and submit this summary with bibliography as part of a 505(b)(2) application. In addition, we encourage submission of all available nonclinical information including any pharmacological data generated with the drug substance and/or drug product.

V. HUMAN PHARMACOKINETICS AND BIOAVAILABILITY SECTION

The bioactivity and/or bioavailability of the active ingredients should be determined at the site of action (gastrointestinal tract). The lipase, amylase, and protease activities should be determined from aspirates from the stomach and duodenum. The data should be obtained under fasting conditions as well as after a standard meal stimulation.

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[6] GRAS listings are included in 21 CFR parts 182 and 582 and are updated each year.

[7] The Agency is developing a draft guidance entitled *Nonclinical Studies for the Development of Pharmaceutical Excipients*. Once that draft guidance has been finalized, it will represent the Agency's current thinking on this topic.

The use of any inactive ingredient in the formulation to prevent or minimize the hydrolysis of the enzymes in the stomach should be supported with in vitro and/or in vivo release data. An appropriate in vitro release test method should be developed.

VI. CLINICAL STUDIES FOR NEW PEPS (SECTION 505(b))

The Agency has determined there is a considerable body of evidence that replacement of pancreatic enzymes has clinical benefit for patients with cystic fibrosis and chronic pancreatitis. (see the *Federal Register* notice that is being published concurrently with this draft guidance). This section summarizes general approaches to the design of clinical studies intended to provide such evidence of effectiveness and safety in support of an NDA for PEPs. The discussion includes guidance on patient populations that should be studied, endpoints (outcome measures) to evaluate efficacy and safety, and suggestions for the design of clinical studies.

A. Considerations for Clinical Trial Development

Currently marketed PEPs differ in their composition, enzymatic activities, formulation, method of manufacture, stringency of quality control during manufacturing, stability, and bioavailability (i.e., bioactivity in the small intestine). These differences have led to highly variable PEP quality and therapeutic performance among manufacturers. For any given manufacturer, such differences over time can lead to batch-to-batch inconsistency and to unacceptable variability in PEP quality and therapeutic performance. With improvements in quality as outlined in the guidance, therapeutic performance may be better predicted from in vitro studies or from in situ measurements of PEP bioactivity in the small intestine.

For NDA approval of any particular PEP, clinical studies should demonstrate a relationship between the extent of clinical benefit and the amount of PEP administered (e.g., empirical demonstration of dose-response relationships in clinical trials).

NDAs filed under section 505(b)(2) of the Act may include published articles along with a bibliography of clinical trials in lieu of clinical data.

B. Patient Populations in Clinical Studies

Two distinct populations have the largest clinical need in practice for PEPs: (1) pediatric and adult patients with cystic fibrosis and (2) adult patients with chronic pancreatitis. Both conditions can cause pancreatic insufficiency and maldigestion, leading to malabsorption of dietary nutrients and subsequent malnutrition. Different dosages of PEPs may be recommended to treat these two populations. ***At a minimum, because cystic fibrosis is primarily a pediatric disease, the efficacy studies in the NDA should include clinical studies in pediatric patients with cystic fibrosis.***

C. Endpoints (Outcome Measures) Efficacy

Although demonstrating a beneficial effect on clinical outcomes is desirable in clinical trials (e.g., weight gain or nutritional status), efficacy can also be demonstrated by showing a meaningful beneficial effect on appropriate pharmacodynamic measures such as steatorrhea. Some examples are provided here:

- Demonstration that administration of the PEP to patients with exocrine pancreatic insufficiency causes a meaningful decrease in stool fat as evaluated in a 72-hour quantitative stool collection

- Demonstration that administration of the PEP to patients with exocrine pancreatic insufficiency causes significantly more responders than in a comparison group (e.g., stool fat originally higher than 14 g/day decreased to less than 7 g/day)

- Demonstration that administration of the PEP to patients with exocrine pancreatic insufficiency causes significantly fewer patients to withdraw from blinded therapy because of steatorrhea than in a comparison group

- Other quantitative endpoints can be considered

D. Safety

Safety variables that should be assessed in clinical trials with PEPs include symptoms and signs of malabsorption, such as manifestations of steatorrhea (bulky, oily, foul smelling stools); complaints of bloating; flatus; abdominal pain; loose and frequent stools; overt diarrhea; blood in the stool; and uric acid elevations.

With regard to safety, we note that the etiology of fibrosing colonopathy has not been completely elucidated. In an effort to minimize development of fibrosing colonopathy that has been assumed to be related to high doses of PEPS, the FDA, in conjunction with the Cystic Fibrosis Foundation (CFF), recommends a starting dose titration of 1500-2500 lipase units/kg/meal, not to exceed 6000 lipase units/kg/meal (Borowitz et al., 1995). This dosing recommendation, applicable to any formulation, was made on the basis of concern over dose-related colonic strictures in cystic fibrosis and the likelihood that maximal efficacy is achieved at the recommended ceiling dose.

E. Design

The clinical studies confirming efficacy of the specific PEP can be (1) parallel, (2) randomized withdrawal, or (3) crossover designs. The designs of these studies for PEP products are discussed below. Other designs, such as those in which patients are challenged with increases in dietary fat, can also be considered.

The clinical studies confirming efficacy of the specific PEP should include appropriate controls, such as dose-comparison controls, or active treatment controls. Placebo may be appropriate with a rescue protocol to protect patients. As noted in the sections below, if a placebo is not used (such as in a comparison of two doses of a PEP, or in a comparison of one PEP with another (e.g., an active control)), differences between treatments should be demonstrated to help interpret results. If desired, the efficacy and dose response of the PEP can be demonstrated in the same study.

Duration of the entire trial could be days to 2 to 3 weeks, depending on the design chosen. Blinding and randomization are recommended to reduce bias. Diets may need to be standardized. The total numbers of patients in the study can be between 10 and 25, depending on study design. Two studies are desirable. A single, larger study may also be appropriate.

1. Parallel studies

Studies of a parallel design can be used to demonstrate efficacy of a PEP, such as when the effects of the PEP are compared to other doses of a PEP and/or to another active product (such as another PEP), or placebo.

2. Randomized withdrawal

A randomized withdrawal study should have two phases: a run-in phase and a randomized withdrawal phase. In the run-in phase, patients should be administered the PEP under study and the dose should be adjusted (e.g., titrated) to achieve and stabilize at the desired clinical outcome (e.g., control of stool fat excretion). An open-label design is appropriate for this phase. In the next phase (the withdrawal phase), patients who have apparently responded to the PEP should then be randomized in a double-blind fashion to either continued treatment with the PEP or, as is typical, to placebo. At the end of the withdrawal phase the effects of the two treatments should be compared. For example, the primary efficacy endpoint could be a quantitative measure of stool fat over 72 hours (e.g., the mean change in stool fat or the number of nonresponders who have recurrent steatorrhea). In some cases at the outset of the randomized withdrawal period, it may be desirable to discontinue treatment gradually to avoid sudden onset of symptoms of pancreatic insufficiency.

Patients should be monitored even during the withdrawal phase to allow discontinuation from randomized study treatment if clinically appropriate (e.g., for clinically worrisome diarrhea). Patients who discontinue study treatment can then be given appropriate medical therapies. If prespecified in the protocol, a count of these treatment failures (nonresponders) can be incorporated into the primary efficacy analysis. In such cases, the protocol should define specific discontinuation criteria for patients who fail treatment.

A randomized withdrawal design also can be adapted to incorporate a dose-response evaluation of a PEP. At the outset of the withdrawal phase, for example, patients can be randomized to placebo and to two or more dosage levels of a PEP. The response of patients at the different dosage levels (including placebo) can then be compared. Although inclusion of a placebo arm is

often the most usual and straightforward way of demonstrating efficacy, this arm can sometimes be excluded.

3. Crossover studies

In a crossover study, each patient in the study is treated with all or most of the treatments under investigation, usually in a randomized sequence.

A crossover study allows for a paired statistical analysis of the data (i.e., each patient serves as his or her own control), thereby decreasing the effects of interpatient variability, which otherwise might obscure true drug effects. In general, fewer patients are needed to perform a crossover study than a study of a parallel design. However, because each patient is administered several treatments, each patient's study involvement is longer than in a parallel study. Moreover, sponsors are strongly cautioned that if baseline conditions are not reestablished between treatment periods, or if treatment in one period carries over into the subsequent period or periods, the results likely will not be interpretable using a paired statistical analysis. Although data from the first period could still be analyzed as in a parallel study (unpaired statistical analysis), the main advantage of using a crossover design would have been lost.

In a randomized, two-period, placebo-controlled, cross-over study of a PEP, for example, patients should first be stabilized on existing therapy to establish baseline conditions. Patients should then be randomized to receive one of two treatment sequences: placebo-PEP vs. PEP-placebo. If quantitative determination of stool fat is used as the primary endpoint, each period should last at least 72 hours to allow for adequate collection of stool specimens. Between periods, reestablishment of baseline conditions should be documented.

VII. PEDIATRIC STUDIES FOR PEPS

A significant portion of the target population for PEPs includes pediatric patients with cystic fibrosis, a congenital genetic disease in which there is chronic exocrine pancreatic insufficiency dating from birth. These patients include the majority of pediatric patients with exocrine pancreatic insufficiency. At the time of publication of this guidance, the only PEP approved for use in pediatric cystic fibrosis patients is an immediate-release formulation, and that product is not currently marketed.

Solid dosage forms of PEPs cannot be swallowed by very young pediatric patients. Therefore sponsors are encouraged to develop age-appropriate formulations for this patient population.

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