CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-175Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 022175

COMPLETE RESPONSE

Digestive Care, Inc.
Attention: Tibor Sipos, Ph.D.
President
1120 Win Drive
Bethlehem, PA 18017

Dear Dr. Sipos:

Please refer to your new drug application (NDA) dated October 27, 2008, received October 27, 2008, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Pertzye (pancrelipase) Delayed-Release Capsules.

We acknowledge receipt of your amendments dated December 4, 2008, December 5, 2008, December 8, 2008, December 12, 2008, December 15, 2008, March 13, 2009, March 17, 2009, June 3, 2009, June 11, 2009, June 24, 2009, June 29, 2009, July 10, 2009, July 30, 2009, July 31, 2009, August 11, 2009, August 18, 2009, March 25, 2010, and March 31, 2010.

We also acknowledge your February 17, 2010, March 24, 2010, and July 29, 2010 submissions which constituted a complete response to our August 27, 2009, action letter. We further acknowledge receipt of your amendments dated September 27, 2010 and November 10, 2010. These submissions received a preliminary review for this action. You may incorporate these amendments by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

1. The (b) (4) DMF (b) (4) has been reviewed in support of NDA 022175 and found to contain deficiencies. A letter dated October 27, 2010, was sent to (b) (4) listing several deficiencies regarding the drug substance manufacturing process. The Agency conveyed additional information requests at a face-to-face meeting held on November 15, 2010, with representatives from (b) (4). (b) (4) should address all deficiencies by directly submitting information to the DMF, or, if the information was previously submitted, then by specific reference to the appropriate submissions. You should notify us when (b) (4) has submitted the requested information. Satisfactory resolution of the deficiencies identified is required before this application may be approved.

2. You have provided retrospective validation reports for the Pertzye drug product manufacturing process. The retrospective validation does not take into account manufacturing development, manufacturing changes, and changes in analytical testing techniques. Since 2004, you have introduced changes in the manufacturing process of the MS-16 strength and changes in analytical testing techniques. Furthermore, no validation data were submitted for the new (b) (4) MS-8 strengths. Given these issues and the complexity of protein products, a prospective process validation should be conducted, to demonstrate your ability to consistently manufacture a product that meets the expected quality standards. You should provide prospective process validation reports with all relevant supporting data for the (b) (4), MS-8 and MS-16 strengths, to demonstrate that your process is adequately controlled.

3. In regard to your release and stability acceptance criteria, we have the following comments:

    a. You did not establish an upper limit for the acceptance criteria for the protease and amylase potency assays for release and stability testing. Lack of an upper limit would allow for wide excursions of amylase and protease potencies, beyond the results obtained on the clinical trial material and on your historical lots. In order to ensure consistency of the drug product amylase and protease potencies, you should establish and justify release and stability acceptance ranges for amylase and protease.

    b. You have established a lipase stability acceptance range of (b) (4) activity, which is significantly different from the acceptance range (b) (4) activity) you have established for lot release. The (b) (4) acceptance range is not adequately justified by the data provided in the application and it is unclear how the proposed limits relate to your clinical experience. The lipase activity result you have obtained for lot PC-6H05B is significantly different (b) (4) than for lots PC-6K09B and PC-7A01B. Furthermore, from the data you have provided, it appears that lipase activity shows (b) (4) during storage of the MS-16 drug product. Provide the following:

        i. An explanation addressing the fluctuation in lipase activity.

        ii. Additional justification for the proposed limits with supporting data, or a revision of the lipase stability acceptance criterion, as appropriate.

4. You are requesting a (b) (4) expiry for the (b) (4) MS-8 drug products. However, you have submitted only nine months of real-time stability data in the application. Expiration dating of protein products is based on real-time, real temperature stability data. Provide real-time stability data that support your requested expiry dating or revise the dating period.

5. You are proposing a qualification program for your drug substance reference standard that includes release testing assays. The acceptance criteria you have established for the qualification program are the same acceptance criteria you are using for release testing. Use of the release acceptance criteria could potentially allow for product characteristics in the new reference standard to be out of trend with the desired or expected product characteristics,

thereby introducing drift into the product over time. You should update your reference standard qualification program, as follows:

a. Your acceptance criteria should be (b) (4) the release acceptance criteria and should be based on your historical trend results as well as on the results of testing conducted on the clinical trial material.

b. Establish upper limits for the protease and amylase specifications.

c. Incorporate the RP-HPLC assay in your reference standard qualification protocol.

6. Your annual stability program for the drug product provides for one lot of material to be entered in the stability program at the proposed storage conditions. However, the purpose of the annual stability program is not to confirm stability at the intended storage conditions, but rather to demonstrate that routine changes such as rotation of operators or minor equipment changes do not have a significant impact on the stability profile of the product. Stability studies conducted under the recommended storage conditions may not be adequate to address this issue because little or no degradation is likely to occur under these conditions even when there is a problem with product stability. You should incorporate accelerated and/or stressed stability studies in your annual stability program for the drug product.

7. You have provided development and validation studies in support of a new RP-HPLC assay to be performed for release and stability testing of Pertzye. However, it is not clear whether the assay has been implemented. Provide available release and stability data that include the RP-HPLC assay. Furthermore, you should address or provide information for the following items:

a. You have provided acceptance criteria for six enzyme peaks and for several impurities. However, you have not established acceptance criteria for the appearance of new peaks or for minor peaks that are not included in your acceptance criteria. Lack of monitoring for new impurities or minor peaks would allow for changes in the purity/impurity profile of your product. You should update your acceptance criteria appropriately.

b. You have established stability acceptance criteria based on the results obtained on two 30-month old lots. These acceptance criteria would allow for significant decreases in enzyme content, and are not adequately justified. Provide a justification with supporting data for your stability acceptance criteria for the RP-HPLC assay or revise as appropriate.

c. In your validation studies you have not evaluated percentage recovery of the protein samples after chromatography. Protein retention on the chromatography column could provide inaccurate assay results. Additionally, there are no studies that evaluate the lifetime and performance of the chromatography column. Use of the column at the end of the lifetime might result in inadequate separation of protein samples and altered elution profiles that would provide inaccurate assay results. You

should provide information on sample recovery and validation studies supporting column performance and reuse.

d. You have not submitted the method description for the assay conducted at Digestive Care, Inc. (DCI). Since DCI is the site at which the RP-HPLC assay used for release and stability testing will be conducted, you should provide the DCI method description and Standard Operating Procedure.

e. We have the following comments regarding the (b) (4) method:

i. You are using a purified elastase standard curve to determine the quantity of the enzymes you have selected to report. However, you have not included a drug product reference standard, to be run along with the samples. The reference standard will ensure that the chromatographic profile of the sample is consistent and that no new peaks appear. You should include a reference standard to be run in each assay.

ii. You have provided information on how to calculate quantities of the enzymes you have selected to report. However, there is no description of how the impurity levels should be quantified. Without this information, the peak impurity levels cannot be evaluated. You should update your method to include a description of the procedures you will use to quantify impurity levels.

iii. In your method, you state that samples and (b) (4) are stable for (b) (4). However, the study you have conducted to evaluate sample stability was carried out for two days, and no study was conducted to evaluate the stability of the (b) (4). The data you have submitted do not support stability of the sample or (b) (4) for the period of time indicated in the method. Therefore, you should provide the results of studies that demonstrate that samples and (b) (4) are stable for (b) (4), or revise your method based on the supporting data you currently have.

CLINICAL PHARMACOLOGY

8. The validation reports for the lipase (TMV-047) and protease (TMV-043) assay methods, submitted on February 15, 2010, are not acceptable to fulfill Clinical Pharmacology Deficiency #19 in the complete response letter dated August 27, 2009. Furthermore, the applesauce compatibility study report (RR-166) is not considered complete.

a. We recommend that you evaluate in-process assay performance during actual study sample runs by simultaneously running quality control samples. For additional information regarding the preparation of adequate assay performance reports, we refer you to Section C. Application to Routine Drug Analysis (page 17) in FDA's Guidance for Industry: Bioanalytical Method Validation, located at: (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf).

b. We also recommend that you submit a comprehensive applesauce compatibility report so that we may complete our clinical pharmacology review. For example, the methods section needs to include information in sufficient detail such that an independent laboratory could reproduce your results. At least three product batches need to be tested for each product strength.

FACILITY INSPECTIONS

9. During an inspection of a manufacturing facility referenced in this application, (b) (4) conducted between (b) (4) and (b) (4) FDA investigators conveyed deficiencies to a representative of the facility. (b) (4) response dated (b) (4), addressing the deficiencies listed on FDA form 483 dated (b) (4), was not adequate. Satisfactory resolution of these deficiencies is required before this application may be approved.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

As described in our letter dated March 19, 2009, in accordance with section 505-1 of the FDCA, we have determined that a risk evaluation and mitigation strategy (REMS) is necessary for Pertzye (pancrelipase) Delayed-Release Capsules to ensure that the benefits of the drug outweigh the known risk of fibrosing colonopathy associated with higher doses of pancreatic enzyme products (PEPs), and the theoretical risk of transmission of viral disease to patients.

We acknowledge the submission of your proposed REMS on July 31, 2009, which contains a Medication Guide and a timetable for submission of assessments of the REMS. We will continue discussion of your proposed REMS after your complete response to this action letter has been submitted.

For administrative purposes, designate all submissions related to the proposed REMS "**PROPOSED REMS-AMENDMENT for NDA 022175**."

If you do not submit electronically, please send 5 copies of your REMS-related submissions.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
    - Present tabulations of the new safety data combined with the original NDA data.
    - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
    - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

POSTMARKETING REQUIREMENTS UNDER 505(o)(3)

As described in our letter dated August 27, 2009, we have determined that if this application is approved, you will be required to conduct postmarketing studies for Pertzye (pancrelipase) Delayed-Release Capsules to assess a known serious risk of fibrosing colonopathy and an unexpected serious risk of transmission of viral disease to patients taking Pertzye (pancrelipase) Delayed-Release Capsules, as follows:

1. A 10-year, observational study to prospectively evaluate the incidence of fibrosing colonopathy in patients with cystic fibrosis treated with Pertzye (pancrelipase) Delayed-Release Capsules in the US and to assess potential risk factors for the event.

2. A 10-year, observational study to prospectively evaluate the risk of transmission of selected porcine viruses in patients taking Pertzye (pancrelipase) Delayed-Release Capsules.

Any additional specific details for these required postmarketing studies, including a timetable and annual reporting requirements, will be described more fully in the approval letter for this application, if it is approved.

If you complete one or both of these studies prior to re-submitting your application, you may include the final report(s) and relevant data sets in your complete response submission to facilitate review of the information.

ADDITIONAL COMMENTS

Although the following comments are not approvability issues at this time, we request that you address them in your resubmission.

1. You responded on March 31, 2010 to the Agency's request on March 22, 2010, for further exploration and/or explanation of the causes for the loss of lipase activity during the dissolution testing. You indicated that 1) you have already explored various conditions (under Study No. RR-083) and 2) the Agency, in a letter dated May 7, 2009, had already accepted your proposed dissolution specifications Q=(b) (4) at 30 minutes.

   The Agency needs more information in order to make a final decision regarding this issue. Based on the results of Study No. RR-083, you selected fortified intestinal fluid as a medium for dissolution testing in which the substrates were added to stabilize the pancrelipase, i.e., olive oil for lipase, casein for protease, and starch for amylase (assay method TM-6013).

   However, you have not determined in your assay method (TM-6013) if the amount of olive oil added to the fortified intestinal fluid will later affect the determination of lipase activity when titrating the fatty acid liberated from the substrate, olive oil, after being digested by lipase.

   Therefore, your proposed Q=(b) (4) at 30 minutes is not considered fully justified. Please justify the use of fortified intestinal fluid as a dissolution medium vs. the use of the USP lipase assay method.

2. Please consider conducting dissolution testing using the USP dissolution method, i.e., in the acid stage for one hour and then transferring the contents to the buffer stage.

3. Provide individual and mean dissolution data (at 10, 20, and 30 minutes in the buffer stage) and mean dissolution profiles of the (b) (4) proposed strengths.

4. Propose an acceptance criterion for the dissolution of your products.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Elizabeth Ford, Regulatory Project Manager, at (301) 796-0193.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JULIE G BEITZ
01/27/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022175 **COMPLETE RESPONSE**

Digestive Care, Inc.
Attention: Tibor Sipos, Ph.D.
President
1120 Win Drive
Bethlehem, PA 18017-7059

Dear Dr. Sipos:

Please refer to your new drug application (NDA) dated October 27, 2008, received October 27, 2008, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Pancrecarb (pancrelipase) Delayed-Release Capsules.

We acknowledge receipt of your amendments dated December 4, 2008, December 5, 2008, December 8, 2008, December 12, 2008, December 15, 2008, March 13, 2009, March 17, 2009, June 3, 2009, June 11, 2009, June 24, 2009, June 29, 2009, and July 10, 2009.

We also acknowledge receipt of your amendments dated July 30, 2009, July 31, 2009, August 11, 2009, and August 18, 2009, which were not reviewed for this action. You may incorporate applicable sections of these amendments by specific reference as part of your response to the deficiencies cited in this letter.

We have completed the review of your application, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

1. Your release testing program is inadequate. Specifically, we have identified the following deficiencies:

    a. You have not included an analytical test to control for product-related and process-related impurities. Product and process-related impurities should be monitored and appropriate acceptance criteria, based on process capability, manufacturing history and clinical experience should be developed and implemented. An analytical methodology such as, but not limited to, HPLC would be suitable to assess the purity of your product.

    b. You have not included analytical tests to monitor particle size, target weight of pellets/capsule and capsule disintegration time. Appropriate analytical methodologies should be used and acceptance criteria established.

c. Your acceptance limit for dissolution is not adequate. Revise the acceptance limit to reflect manufacturing history, clinical experience and USP guidelines for dissolution.

2. Your stability program does not provide assurance that product stability is adequately controlled. Specifically, we have identified the following deficiencies:

   a. You have not included analytical techniques that monitor product degradation such as, but not limited to, HPLC.

   b. The acceptance criterion for lipase activity should be revised to include an upper and lower limit.

   c. The stability data you have provided indicate that some drug product lots show a clear (b) (4) trending in the dissolution profile over a 12-month period whereas, some other lots maintain a stable dissolution profile. Provide an explanation for these inconsistencies in the stability data.

   d. You are currently reporting (b) (4) content as a combination of all (b) (4) measured. Acceptance criteria for each of the (b) (4) should be provided separately.

   e. Expiry dating for a protein product is based on real-time and real-temperature stability data. You have not provided real-time stability data to support a 24 month expiry.

   f. Provide your rationale for using (b) (4), in addition to gelatin capsules, and justify why additional stability or clinical data are not necessary.

   g. You have not provided a study that addresses the stability of the product once the final container is opened in the pharmacy or by the patient. Provide forced degradation studies (i.e., photostability, moisture conditions, etc.) conducted on the drug product to support in-use stability of drug product.

   h. Update your stability protocol to include (b) (4) testing at all test stations.

3. You have not provided sufficient information to the Agency to evaluate the (b) (4) steps in your manufacturing process. Provide studies conducted and documentation of procedures you have in place to support (b) (4).

4. You are (b) (4) drug substances manufactured by different processes (1206 and 1208) to achieve a defined target lipase activity. However, you have not provided sufficient information to evaluate whether the (b) (4) step in your manufacturing process will result in a homogeneously (b) (4) drug substance. Provide validation studies that address the

homogeneity of the [redacted] drug substance used to manufacture [redacted] MS-8, and the homogeneity of the [redacted] drug substance used to manufacture MS-16.

5. Due to the critical role of [redacted] in lipase activity, adequate control of [redacted] activity must be ensured in drug product. Provide information that demonstrates you have control of [redacted] activity in drug substance and product.

6. You have not submitted sufficient information in the NDA to evaluate your qualification program for the lipase olive oil substrate. Provide qualification results for olive oil testing, and establish and justify specifications for critical olive oil components.

7. Provide a description of your qualification program for incoming 1206 and 1208 drug substances.

8. We recommend that an internal reference standard that reflects the drug product commercial manufacturing process be used, in addition to the pancrelipase drug substance reference standard, in all release and stability testing. Develop a rigorous qualification program aimed at ensuring that the quality attributes of the internal reference standard are maintained when new internal reference standards are required and manufactured.

9. Due to the potential inconsistencies and reliance on the USP lipase reference standard, we recommend the development and implementation of a method that includes a measurement of absolute units to ensure accurate and consistent lipase activity for the working reference standard.

10. In regard to your analytical methodologies, we have the following comments:

    a. The assessment of linearity for the lipase and protease assays is conducted using [redacted] data points. We recommend a minimum of 5 data points for determination of assay linearity.

    b. Clarify your acceptance criteria for lipase assay linearity.

    c. To support validation of [redacted] assay precision, clarify the amounts of [redacted] and [redacted] used during assay validation.

11. Provide detailed information regarding the chemistry, manufacturing, and controls for the cellulose acetate phthalate and diethyl phthalate used for [redacted] of the product.

12. Provide the drug product release test sampling plans.

13. Provide a comparison of the formulation of the To be Marketed Product (TbMP) and the Currently Marketed Product.

14. We do not have sufficient information to evaluate your process validation. Provide the following information:

    a. The process validation report, with all relevant supporting data to demonstrate that your process is adequately controlled.

    b. Clarify the method used to assess the yield in (b) (4) of drug product manufacturing.

15. Provide representative vendor Certificates of Analysis (COAs) and your testing results of the excipients used in the manufacturing of (b) (4), MS-8 and MS-16.

16. The DMF you have referenced for the (b) (4) Ink, DMF (b) (4), is closed. Provide chemistry, manufacturing, and controls information, including (b) (4) content, for (b) (4) Ink.

17. We noticed discrepancies between the manufacturing dates of drug product lots, and the dates the COAs were signed. In some cases, over two years elapsed between manufacturing and COA sign-off. Explain these discrepancies.

18. The (b) (4) DMF # (b) (4) has been reviewed in support of your NDA and found to contain deficiencies. A letter will be sent to (b) (4) listing the deficiencies. (b) (4) should address the deficiencies and update the DMF by directly submitting information to the DMF. Please notify us when (b) (4) has submitted the requested information.

CLINICAL PHARMACOLOGY

19. The submitted applesauce study (Protocol #080705) is not acceptable because the lipase assay method was not adequately validated (see PRODUCT QUALITY Comment #10 above). We recommend that you repeat the applesauce study with newly validated analytical methods and submit the results for review. The use of applesauce as a mixing medium to facilitate product administration will be labeled based on the results of the repeat study, if found acceptable.

CLINICAL

20. We were unable to determine the efficacy of the (b) (4) MS-8 formulations because the studies submitted (b) (4) were not adequate to demonstrate the effectiveness of the (b) (4) MS-8 formulations. In addition, comparability of the (b) (4) formulations (b) (4) MS-8, MS-16) relative to one another was not shown by the information provided in the NDA submission.

(b) (4)

(b) (4)

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

21. As described in our letter dated March 19, 2009, in accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Pancrecarb (pancrelipase) Delayed-Release Capsules and other porcine-derived pancreatic enzyme products (PEPs) to ensure that the benefits of the drug outweigh the risk of fibrosing colonopathy associated with higher doses of PEPs, and the theoretical risk of transmission of viral disease to patients.

    We acknowledge the submission of your REMS documents on July 31, 2009. Once FDA finds the content of your REMS acceptable and determines that the application can be approved, we will include these documents as an attachment to the approval letter that includes the REMS.

    Under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. You should submit marked up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

    "Dispense the enclosed Medication Guide to each patient." or

    "Dispense the accompanying Medication Guide to each patient."

    Prominently identify submissions related to the proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

    NDA 022175
    PROPOSED REMS-AMENDMENT

    If you do not submit electronically, please send 5 copies of your REMS-related submissions.

LABELING

We reserve additional comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html.

FACILITY INSPECTIONS

During recent inspections of (b) (4) and Digestive Care, Inc, the manufacturing facilities for this application, our field investigators conveyed deficiencies to the representatives of each facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
    - Present tabulations of the new safety data combined with the original NDA data.
    - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
    - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known serious risk of fibrosing colonopathy and the unexpected serious risk of transmission of viral disease to patients taking Pancrecarb (pancrelipase) Delayed-Release Capsules.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that, if this application is approved, you will be required, pursuant to section 505(o)(3) of the FDCA, to conduct:

1. A 10 year, observational study to prospectively evaluate the incidence of fibrosing colonopathy in patients with cystic fibrosis treated with Pancrecarb (pancrelipase) Delayed-Release Capsules in the US and to assess potential risk factors for the event.

2. A 10 year, observational study to prospectively evaluate the risk of transmission of selected porcine viruses in patients taking Pancrecarb (pancrelipase) Delayed-Release Capsules.

The specific details of these required postmarketing studies will be described more fully in the approval letter for this application, if it is approved.

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's *Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants*, May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Elizabeth Ford, Regulatory Project Manager, at (301) 796-0193.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JULIE G BEITZ
08/27/2009