

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-175Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 022175

SUPPL #

HFD # 180

Trade Name Pertzye

Generic Name pancrelipase

Applicant Name Digestive Care, Inc.

Approval Date, If Known May 18, 2012

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

Investigation #2

!

YES

! NO

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

=====

Name of person completing form: Jagjit Grewal, M.P.H.

Title: Senior Regulatory Health Project Manager

Date: May 11, 2012

Name of Office/Division Director signing form: Julie Beitz, M.D.

Title: Director, Office of Drug Evaluation III

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

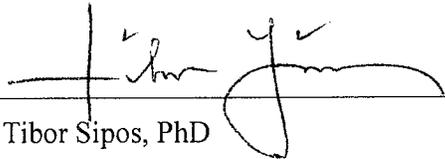
JAGJIT S GREWAL
05/16/2012

JULIE G BEITZ
05/16/2012

DEBARMENT CERTIFICATION

FDA makes available a separate list of firms or persons debarred pursuant to the debarment provisions of the Federal Food, Drug, and Cosmetic Act located at http://www.fda.gov/ora/compliance_ref/debar/default.htm. The names of principal investigators and subinvestigators involved in clinical research sponsored by Digestive Care, Inc. have been checked against this list to assure that investigators are permitted to conduct clinical investigations for the company.

Digestive Care, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



Tibor Sipos, PhD
President, Digestive Care, Inc.

11-25-2008

Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 022175 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Pertzye Established/Proper Name: pancrelipase Dosage Form: Delayed-Release Capsules		Applicant: Digestive Care, Inc. Agent for Applicant (if applicable):
RPM: Jagjit Grewal, Matthew Scherer, Elizabeth Ford		Division: Division of Gastroenterology & Inborn Errors Products
<p><u>NDA's:</u> NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input checked="" type="checkbox"/> If no listed drug, check here and explain: Based on the literature.</p> <p>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</p> <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check: 5/17/12</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p> <p>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p>
❖ User Fee Goal Date Action Goal Date (if different)		5/18/2012 5/17/2012
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (<i>specify type and date for each action taken</i>)		CR 1/27/2011, CR 8/27/2009
❖ Promotional Materials (<i>accelerated approvals only</i>) Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance www.fda.gov/cder/guidance/2197dft.pdf). If not submitted, explain _____		<input type="checkbox"/> Received

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application ² Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): Type 7 <input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC NDAs: Subpart H BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart I Subpart H <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC Comments: _____	
❖ Date reviewed by PeRC (<i>required for approvals only</i>) If PeRC review not necessary, explain: _____	4/4/2012
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)	<input type="checkbox"/> Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input checked="" type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

² All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified <u>N/A; no RLD</u> 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist ³	5/17/2012
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	AP 5/17/2012, CR 1/24/2011, CR 8/27/2009
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> • Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	5/11/2012
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	10/27/2008
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	Ultresa 3/1/2012, Zenpep 7/13/2011, Pancreaze 4/12/2010
❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> None

³ Fill in blanks with dates of reviews, letters, etc.
Version: 9/5/08

<ul style="list-style-type: none"> Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	5/11/2012
<ul style="list-style-type: none"> Original applicant-proposed labeling 	7/31/2009
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	Ultresa 3/1/2012, Zenpep 6/15/2011, Pancreaze 4/12/2010
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date at upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> Most-recent division proposal for (only if generated after latest applicant submission) 	
<ul style="list-style-type: none"> Most recent applicant-proposed labeling 	5/11/2012
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input checked="" type="checkbox"/> RPM 12/18/2008 <input checked="" type="checkbox"/> DMEPA 2/23/2012, 5/8/2009 <input checked="" type="checkbox"/> DRISK 4/9/2012 <input checked="" type="checkbox"/> DDMAC 4/12/2012, 12/9/2010 <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews: SEALD 4/17/2012 OBP RPM 4/17/2012
❖ Proprietary Name <ul style="list-style-type: none"> Review(s) (<i>indicate date(s)</i>) Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) 	2/10/2012, 9/24/2009, 3/19/2009 2/10/2012, 9/24/2009, 4/8/2009
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	12/19/2008
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	<input type="checkbox"/> Not a (b)(2) 3/26/2012
❖ 505(b)(2) Assessment (<i>indicate date</i>)	<input type="checkbox"/> Not a (b)(2) 5/17/2012
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included 5/16/2012
❖ Application Integrity Policy (AIP) Status and Related Documents www.fda.gov/ora/compliance_ref/aip_page.html	
<ul style="list-style-type: none"> Applicant in on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>) <ul style="list-style-type: none"> Date reviewed by PeRC April 4, 2012 If PeRC review not necessary, explain: Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable

⁴ Filing reviews for other disciplines should be filed behind the discipline tab.
Version: 9/5/08

❖ Outgoing communications (<i>letters (except previous action letters), emails, faxes, telecons</i>)	5/15/2012, 5/4/2012, 4/27/2012, 4/20/2012, 4/13/2012, 4/12/2012, 4/10/2012, 3/30/2012, 3/29/2012, 3/7/2012, 2/24/2012, 2/23/2012, 2/17/2012, 1/20/2012, 1/31/2012, 12/2/2011, 9/15/2011, 10/27/2010, 9/23/2010, 8/21/2010, 7/10/2009, 6/29/2009, 6/15/2009, 5/28/2009, 5/7/2009, 4/9/2009, 4/8/2009, 3/19/2009, 3/2/2009, 2/27/2009, 1/8/2009, 12/18/2008, 12/3/2008, 11/10/2008, 7/16/2008
❖ Internal memoranda, telecons, etc.	5/17/2012, 11/3/2009, 7/13/2009, 6/24/2009
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> N/A or no mtg 6/22/2011
• Pre-NDA/BLA meeting (<i>indicate date</i>)	<input type="checkbox"/> No mtg 10/31/2007, 2/5/2007, 9/11/2006, 6/23/2005
• EOP2 meeting (<i>indicate date</i>)	<input checked="" type="checkbox"/> No mtg
• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None 5/17/2012, 1/27/2011, 8/27/2009
Division Director Summary Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 5/17/2012, 1/27/2011, 8/27/2009
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 3 PMRs & 15 PMCs 5/16/2012
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	See CDTL reviews
• Clinical review(s) (<i>indicate date for each review</i>)	12/23/2011, 1/14/2011, 8/27/2009
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	See 8/27/2009 Clinical Review, page 12
❖ Clinical reviews from other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None PMHS 3/6/2012
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed

⁵ Filing reviews should be filed with the discipline reviews.
Version: 9/5/08

❖ Risk Management	<input type="checkbox"/> None
<ul style="list-style-type: none"> Review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) REMS Memo (<i>indicate date</i>) REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>) 	3/19/2009 7/31/2009
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested Review: 6/26/2009 Letters: 6/26/2009, 3/27/2009
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 12/16/2011 (NAD), 7/21/2009, 11/21/2008
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 4/20/2012, 1/13/2011, 8/26/2009, 6/9/2009
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
<ul style="list-style-type: none"> ADP/T Review(s) (<i>indicate date for each review</i>) Supervisory Review(s) (<i>indicate date for each review</i>) Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 8/25/2009 <input checked="" type="checkbox"/> None <input type="checkbox"/> None 6/19/2009
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None requested
CMC/Quality <input type="checkbox"/> None	
❖ CMC/Quality Discipline Reviews	
<ul style="list-style-type: none"> ONDQA/OBP Division Director Review(s) (<i>indicate date for each review</i>) Branch Chief/Team Leader Review(s) (<i>indicate date for each review</i>) CMC/product quality review(s) (<i>indicate date for each review</i>) BLAs only: Facility information review(s) (<i>indicate dates</i>) 	<input type="checkbox"/> None <input type="checkbox"/> None 5/16/2012, 1/21/2011 <input type="checkbox"/> None 4/17/2012, 1/20/2011, 8/25/2009 <input type="checkbox"/> None

<ul style="list-style-type: none"> ❖ Microbiology Reviews <ul style="list-style-type: none"> • NDAs: Microbiology reviews (sterility & pyrogenicity) <i>(indicate date of each review)</i> • BLAs: Sterility assurance, product quality microbiology <i>(indicate date of each review)</i> 	<p>2/3/2012, 6/14/2011, 1/26/2011, 5/13/2009</p> <p><input type="checkbox"/> Not needed</p>
<ul style="list-style-type: none"> ❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i> ONDQA Dissolution Review 	<p><input type="checkbox"/> None 4/22/2012, 12/9/2010, 7/22/2009, 4/27/2009, 12/12/2008</p>
<ul style="list-style-type: none"> ❖ Environmental Assessment (check one) (original and supplemental applications) 	
<ul style="list-style-type: none"> <input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i> 	
<ul style="list-style-type: none"> <input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i> 	
<ul style="list-style-type: none"> <input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i> 	
<ul style="list-style-type: none"> ❖ NDAs: Methods Validation 	<p><input type="checkbox"/> Completed</p> <p><input type="checkbox"/> Requested</p> <p><input type="checkbox"/> Not yet requested</p> <p><input checked="" type="checkbox"/> Not needed</p>
<ul style="list-style-type: none"> ❖ Facilities Review/Inspection 	
<ul style="list-style-type: none"> • NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date)</i> 	<p>Date completed: 3/8/2012</p> <p><input checked="" type="checkbox"/> Acceptable</p> <p><input type="checkbox"/> Withhold recommendation</p>
<ul style="list-style-type: none"> • BLAs: <ul style="list-style-type: none"> ○ TBP-EER ○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) <i>(date completed must be within 60 days prior to AP)</i> 	<p>Date completed:</p> <p><input type="checkbox"/> Acceptable</p> <p><input type="checkbox"/> Withhold recommendation</p> <p>Date completed:</p> <p><input type="checkbox"/> Requested</p> <p><input type="checkbox"/> Accepted <input type="checkbox"/> Hold</p>

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/s/

JAGJIT S GREWAL
05/17/2012

Grewal, Jagjit

From: Glen Park [gpark@targethealth.com]
Sent: Thursday, May 17, 2012 11:45 AM
To: Grewal, Jagjit
Subject: RE: NDA 022175 Pertzze (pancrelipase) - PMC revision
Attachments: emfinfo.txt

Hello Jagjit,

DCI accepts the changes and has not comments.

Best regards,

Glen

From: Grewal, Jagjit [mailto:Jagjit.Grewal@fda.hhs.gov]
Sent: Thursday, May 17, 2012 11:34 AM
To: Glen Park
Cc: Grewal, Jagjit
Subject: NDA 022175 Pertzze (pancrelipase) - PMC revision
Importance: High

Hello Glen,

Reference is made to your New Drug Application submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Pertzze (pancrelipase) Delayed-Release Capsules. We also refer to your correspondence dated May 15, 2012, providing your concurrence with FDA's proposed postmarketing commitments (PMCs), postmarketing requirements (PMRs), and associated milestone dates.

FDA is proposing additional revisions to the drug product dissolution testing PMC #18 as shown below (text added is underlined and text deleted is ~~struckthrough~~). Please review the change and provide your concurrence by this afternoon, May 17, 2012.

For the final dissolution method and acceptance criterion for Pertzze Delayed-Release Capsules:

- a. Follow USP method for dissolution testing, Method <711>, to incubate the product (n=12 capsule units) in the acid stage for 1 hour and then transfer the contents to the buffer stage. Collect a portion of buffer solution at several times points, e.g., 10 minutes, 20 minutes and 30 minutes. Proceed as directed ~~for~~ to assay for lipase activity. Collect additional dissolution profile data from at least 3 production batches of each capsule strength, ~~MS-8 and MS-16~~ containing either 8000 or 16,000 USP units of lipase. Use the dissolution data from these production batches to set the buffer stage dissolution acceptance criterion for your product.
- b. Submit the final report with the complete dissolution data (individual, mean, min, max, and plots, n=12 capsule units) for both ~~the MS-8 and MS-16~~ capsule strengths and a proposal for the buffer stage dissolution acceptance criterion for Pertzze Delayed-Release Capsules, as a prior approval supplement.

Final Report Submission by May 2013

Please acknowledge receipt of this correspondence. I can be reached at the below phone number or via email with any questions

Jagjit Grewal, M.P.H.

Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/OND/ODE III
Food & Drug Administration

Phone: (301) 796-0846 || Fax: (301) 796-9905

Email: Jagjit.Grewal@fda.hhs.gov

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/s/

JAGJIT S GREWAL
05/17/2012

Grewal, Jagjit

From: Grewal, Jagjit
Sent: Tuesday, May 15, 2012 10:26 AM
To: 'Glen Park'
Cc: Grewal, Jagjit
Subject: NDA 022175 Pertzye (pancrelipase) - PMR/PMC communication

Importance: High

Attachments: NDA 022175 Pertzye PMRs-PMCs .doc

Hello Glen,

Reference is made to your New Drug Application submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Pertzye (pancrelipase) Delayed-Release Capsules. We also refer to your email correspondences dated April 13, 2012, April 23, 2012, April 30, 2012, and May 4, 2012, containing your milestone dates and concurrence with FDA's proposed postmarketing commitments (PMCs) and postmarketing requirements (PMRs).

The attached document summarizes all discussed PMCs and PMRs and includes the agreed upon milestone dates. In addition, note that the drug product dissolution testing PMCs issued to you May 4, 2012 have been consolidated into a single PMC #18 in the attached document. Please review the attached information and formally submit your concurrence with the listed PMRs/PMCs and milestone dates to the NDA by May 16, 2012.

Please acknowledge receipt of this correspondence. I can be reached at the below phone number or via email with any questions.



NDA 022175
Pertzye PMRs-PMCs .doc

Jagjit Grewal, M.P.H.
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/OND/ODE III
Food & Drug Administration

Phone: (301) 796-0846 || Fax: (301) 796-9905
Email: Jagjit.Grewal@fda.hhs.gov

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REQUIRED PEDIATRIC ASSESSMENT UNDER PREA

1. Deferred requirement for development of an age appropriate formulation for Pertzye (pancrelipase) Delayed-Release Capsules: Develop an age appropriate formulation to allow for dosing to the youngest, lowest weight pediatric patients, including infants less than 12 months of age who will be administered 2,000 to 4,000 lipase units per 120 mL of formula or per breast-feeding. Submit a supplement by June 30, 2014.

POSTMARKETING REQUIREMENTS UNDER 505(o)

2. 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 U.S. and to assess potential risk factors for the event.

Final Protocol Submission: May 2013
Study Completion Date: July 2023
Final Report Submission: July 2024

3. An observational study to estimate the prevalence of antibody seropositivity to selected porcine viruses in patients taking Pertzye (pancrelipase) Delayed-Release Capsules compared with an appropriate control group.

Final Protocol Submission: May 2013
Study Completion Date: July 2018
Final Report Submission: July 2019

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

Drug Substance:

4. Provide an assessment of the viral inactivation capability of the cleaning agents currently used in the drug substance manufacturing facility.

Final Report Submission by September 1, 2012

5. Develop and validate an infectivity assay for PCV1 (Porcine Circovirus 1).

Final Report Submission by March 1, 2013

6. Establish lot release specifications for PPV (Porcine Parvovirus) and PCV2 (Porcine Circovirus 2) for the drug substance.

Final Report Submission by March 1, 2013

7. Perform additional monitoring of viral load entering the drug substance manufacturing process. The control program should include the selection of human pathogenic viruses for monitoring by qPCR. An appropriate control strategy should be proposed.

Final Report Submission by May 15, 2013

8. Improve the sensitivity of the qPCR assays used for drug substance release testing in order to provide adequate assurance that released drug substance will not contain EMCV, HEV, PEV-9, Reo1/3, Rota, Influenza, VSV-IND, and VSV-NJ viruses. The revised assays, assay validation data, and acceptance criteria should be submitted to the Agency.

Final Report Submission by April 15, 2013

9. Assess the risk to product quality associated with hokovirus, and submit a control strategy for mitigating the risk to product quality.

Final Report Submission by June 1, 2012

10. Revise the animal surveillance program and the risk assessment evaluation for source animals to capture new and emerging viral adventitious agents. The proposed program should include an example using Ebola virus, recently described in pigs from the Philippines, to illustrate how these programs will be implemented.

Final Report Submission by March 15, 2013

11. Provide the results of leachable/extractable studies for the intermediate storage containers, a risk assessment evaluation and a proposed strategy to mitigate the risk to product quality.

Final Report Submission by June 1, 2012

12. Revise release specifications after 30 lots of drug substance 1206 and 1208 lots have been manufactured.

Final Report Submission by May 15, 2013

Drug Product:

13. Revise release and stability specifications after 30 lots of drug product have been manufactured.

Final Report Submission by December 2015

14. Submit a stability protocol used to evaluate and extend the maximum cumulative storage time of the drug substance and drug product. The protocol will provide for placing on stability the first lot of drug product manufactured using drug substance aged beyond drug product manufacturing experience.

Final Protocol Submission by July 2012

15. Establish an expiration date for the RP-HPLC column.

Final Report Submission by July 2015

16. Establish a primary reference standard against which future reference standards will be qualified.

Final Report Submission by December 2012

17. Perform in vitro studies to determine the feasibility of administering the contents of Pertzye (pancrelipase) Delayed-Release Capsules through a gastrostomy tube.

Final Report Submission by June 2013

18. For the final dissolution method and acceptance criterion for Pertzye Delayed-Release Capsules:

- a. Follow USP method for dissolution testing, Method <711>, to incubate the product (n=12 units) in the acid stage for 1 hour and then transfer the contents to the buffer stage. Collect a portion of buffer solution at times, e.g., 10 minutes, 20 minutes and 30 minutes. Proceed as directed for assay for lipase activity. Collect additional dissolution profile data from at least 3 production batches of each strength, MS-8 and MS-16. Use the dissolution data from these production batches to set the buffer stage dissolution acceptance criterion for your product.
- b. Submit the final report with the complete dissolution data (individual, mean, min, max, and plots, n=12) for both the MS-8 and MS-16 strengths and a proposal for the buffer stage dissolution acceptance criterion for Pertzye Delayed-Release Capsules, as a prior approval supplement.

Final Report Submission by May 2013

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/s/

JAGJIT S GREWAL
05/15/2012

Grewal, Jagjit

From: Grewal, Jagjit
Sent: Friday, May 04, 2012 9:15 AM
To: 'Glen Park'
Cc: Grewal, Jagjit
Subject: NDA 022175 Pertzeye (pancrelipase) - FDA Proposed PMCs 5-4-12

Attachments: NDA 022175 - FDA Proposed PMCs 5-4-12.doc

Hello Glen,

Reference is made to your New Drug Application submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Pertzeye (pancrelipase) Delayed-Release Capsules.

Attached is FDA's proposal for additional drug product related postmarketing commitments (PMCs). Please review the attached information and provide your response with the requested milestone dates by May 7, 2012.

Additionally, please acknowledge receipt of this correspondence. I can be reached at the below phone number or via email with any questions.



NDA 022175 - FDA
Proposed PMCs...

Jagjit Grewal, M.P.H.
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/OND/ODE III
Food & Drug Administration

Phone: (301) 796-0846 || Fax: (301) 796-9905
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Please review the following proposed postmarketing commitments (PMCs) for NDA 022175 Pertzye (pancrelipase) Delayed-Release Capsules. Provide milestone dates for each PMC, as requested, or your concurrence with FDA's proposed dates by May 7, 2012.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

1. Conduct dissolution testing following the USP method for Pertzye Delayed-Release Capsules with the product incubating in the acid stage for 1 hour and then transferring the contents to the buffer stage.

Final Report Submission by May 2013

2. To set the final dissolution method and acceptance criterion for Pertzye Delayed-Release Capsules:
 - a. Conduct the requested dissolution study following the USP method and provide additional dissolution profile data (individual, mean, plots, n=12) for both the MS-8 and MS-16 strengths,
 - b. Collect additional dissolution data/profiles from at least 3 production batches per each strength, and
 - c. Submit the report with the complete dissolution data and a proposal for the dissolution acceptance criteria as a prior approval supplement to your NDA

Final Report Submission by [DCI should proposed a date (Month/Year)]

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/s/

JAGJIT S GREWAL
05/04/2012

Grewal, Jagjit

From: Grewal, Jagjit
Sent: Friday, April 27, 2012 4:11 PM
To: 'Glen Park'
Cc: Grewal, Jagjit
Subject: RE: NDA 022175 Pertzye (pancrelipase) - PMC related request for information 4/27/12
Importance: High
Attachments: NDA 022175 - FDA Proposed PMCs 4-20-12_dci accepted.doc

Hello Glen,

Reference is made to your New Drug Application submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Pertzye (pancrelipase) Delayed-Release Capsules. We also refer to your email correspondence dated April 23, 2012, containing your proposed milestone dates for the drug product related postmarketing commitments (PMCs).

We have reviewed your proposed milestone dates and found them to be acceptable with the exception of PMC #1 listed in the attached file. Please provide an earlier final report submission date or justification for why this PMC cannot be fulfilled sooner than January 2018.

Please acknowledge receipt of this correspondence. I can be reached via email or at the below phone number with any questions.

Jagjit Grewal, M.P.H.
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/OND/ODE III
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From: Glen Park [mailto:gpark@targethealth.com]
Sent: Monday, April 23, 2012 12:01 PM
To: Grewal, Jagjit
Subject: RE: NDA 022175 Pertzye (pancrelipase) - FDA Proposed PMCs 4-20-12

Hi Jagjit,

See the attached response from DCI. Let me know if there are any questions.

Glen

From: Grewal, Jagjit [mailto:Jagjit.Grewal@fda.hhs.gov]
Sent: Friday, April 20, 2012 1:20 PM
To: Glen Park
Cc: Grewal, Jagjit
Subject: NDA 022175 Pertzye (pancrelipase) - FDA Proposed PMCs 4-20-12

Hello Glen,

Reference is made to your New Drug Application submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Pertzye (pancrelipase) Delayed-Release Capsules.

Attached is FDA's proposal for drug product related postmarketing commitments (PMCs). Please review the attached information and provide your response with the requested milestone dates by April 24, 2012.

Additionally, please acknowledge receipt of this correspondence. I can be reached at the below phone number or via email with any questions.

Jagjit Grewal, M.P.H.

Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/OND/ODE III
Food & Drug Administration

Phone: (301) 796-0846 || Fax: (301) 796-9905

Email: Jagjit.Grewal@fda.hhs.gov

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Please review the following proposed postmarketing commitments (PMCs) for NDA 022175 Pertzye (pancrelipase) Delayed-Release Capsules. Provide milestone dates for each PMC by April 24, 2012.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

Drug Product:

1. Revise release and stability specifications after 30 lots of drug product have been manufactured.

Final Report Submission by [~~Month/Year~~ January/2018]

2. Submit a stability protocol used to evaluate and extend the maximum cumulative storage time of the drug substance and drug product. The protocol will provide for placing on stability the first lot of drug product manufactured using drug substance aged beyond drug product manufacturing experience.

Final Protocol Submission by [~~Month/Year~~ July/2012]

3. Establish an expiration date for the RP-HPLC column.

Final Report Submission by [~~Month/Year~~ July/2015]

4. Establish a primary reference standard against which future reference standards will be qualified.

Final Report Submission by [~~Month/Year~~ December/2012]

Comment [j1]: DCI's proposed date for this PMC is not acceptable. Please provide an earlier final report submission date or justification for why the PMC cannot be fulfilled earlier than January 2018.

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/s/

JAGJIT S GREWAL
04/27/2012

Grewal, Jagjit

From: Grewal, Jagjit
Sent: Friday, April 20, 2012 1:20 PM
To: 'Glen Park'
Cc: Grewal, Jagjit
Subject: NDA 022175 Pertzye (pancrelipase) - FDA Proposed PMCs 4-20-12

Attachments: NDA 022175 - FDA Proposed PMCs 4-20-12.doc

Hello Glen,

Reference is made to your New Drug Application submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Pertzye (pancrelipase) Delayed-Release Capsules.

Attached is FDA's proposal for drug product related postmarketing commitments (PMCs). Please review the attached information and provide your response with the requested milestone dates by April 24, 2012.

Additionally, please acknowledge receipt of this correspondence. I can be reached at the below phone number or via email with any questions.



NDA 022175 - FDA
Proposed PMCs...

Jagjit Grewal, M.P.H.
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/OND/ODE III
Food & Drug Administration

Phone: (301) 796-0846 || Fax: (301) 796-9905
Email: Jagjit.Grewal@fda.hhs.gov

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Please review the following proposed postmarketing commitments (PMCs) for NDA 022175 Pertzye (pancrelipase) Delayed-Release Capsules. Provide milestone dates for each PMC by April 24, 2012.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

Drug Product:

1. Revise release and stability specifications after 30 lots of drug product have been manufactured.

Final Report Submission by [Month/Year]

2. Submit a stability protocol used to evaluate and extend the maximum cumulative storage time of the drug substance and drug product. The protocol will provide for placing on stability the first lot of drug product manufactured using drug substance aged beyond drug product manufacturing experience.

Final Protocol Submission by [Month/Year]

3. Establish an expiration date for the RP-HPLC column.

Final Report Submission by [Month/Year]

4. Establish a primary reference standard against which future reference standards will be qualified.

Final Report Submission by [Month/Year]

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/s/

JAGJIT S GREWAL
04/20/2012

Grewal, Jagjit

From: Grewal, Jagjit
Sent: Friday, April 13, 2012 12:18 PM
To: 'Glen Park'
Cc: Grewal, Jagjit
Subject: NDA 022175 Pertye (pancrelipase) - FDA Proposed PI, Med Guide, PMRs/PMCs 4-13-12

Importance: High

Attachments: NDA 022175 Pertye - FDA Proposed PI Revisions 4-13-12.doc; NDA 022175 Pertye - FDA Proposed Med Guide Revisions 4-13-12.doc; NDA 022175 - FDA Proposed PMRs-PMCs 4-13-12.doc

Hello Glen,

Reference is made to your New Drug Application submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Pertye (pancrelipase) Delayed-Release Capsules. We also refer to your submission dated April 5, 2012 containing your response to our previous package insert label revisions.

Attached are additional FDA's revisions to your proposed package insert label and Medication Guide. FDA's proposal for postmarketing requirements (PMRs) and postmarketing commitments (PMCs) is also attached. The list of PMRs/PMCs is not all inclusive and additional PMRs/PMCs may be provided to you during the course of our review. Please review the attached information and provide your response by April 19, 2012.

Additionally, please acknowledge receipt of this correspondence. I can be reached at the below phone number or via email with any questions.



NDA 022175 PertyeNDA 022175 Pertye NDA 022175 - FDA
- FDA Propos... - FDA Propos... Proposed PMRs...

Jagjit Grewal, M.P.H.
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/OND/ODE III
Food & Drug Administration

Phone: (301) 796-0846 || Fax: (301) 796-9905
Email: Jagjit.Grewal@fda.hhs.gov

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/s/

JAGJIT S GREWAL
04/13/2012



NDA 022175

INFORMATION REQUEST

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

Dear Dr. Sipos:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pertzye (pancrelipase) Delayed-Release Capsules.

We also refer to your April 11, 2012 submission, containing your response to our request for information dated April 10, 2012.

We have the following comments and information request. We request a written response by April 16, 2012, in order to continue our evaluation of your NDA.

1. We have reviewed your April 11, 2012. response to our information request regarding the lack of real-time stability data for (b) (4)

[REDACTED] (b) (4)

To approve the NDA in its current form, data is required to support (b) (4)

[REDACTED]

If there is no significant decrease in stability during storage, six months of real-time stability data on three lots of each strength (b) (4). The expiration date could be extended with the submission of a post-approval stability protocol. Sufficient in-use stability data should

also be provided in the supplement to support the product's stability under conditions of use by patients.

If you have any questions, call Jagjit Grewal, Regulatory Project Manager, at (301) 796-0846.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology and Inborn
Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

BRIAN K STRONGIN
04/12/2012



NDA 022175

INFORMATION REQUEST

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

Dear Dr. Sipos:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pertzye (pancrelipase) Delayed-Release Capsules.

We also refer to your April 5, 2012 submission, containing your revised carton and container labeling in response to our request for information dated March 29, 2012.

We have the following comments and information request. We request a written response by April 12, 2012, in order to continue our evaluation of your NDA.

1. You are proposing (b) (4) the drug product container closure; a 250 and 100 capsule/bottle for commercial distribution (b) (4). You have provided stability data to support the proposed shelf life for the 250 and 100 capsule/bottle configurations, (b) (4).

The post-approval annual stability commitment should be updated to (b) (4).

If you have any questions, call Jagjit Grewal, Regulatory Project Manager, at (301) 796-0846.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology and Inborn
Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

BRIAN K STRONGIN
04/10/2012



NDA 022175

INFORMATION REQUEST

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

Dear Dr. Sipos:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pertzye (pancrelipase) Delayed-Release Capsules.

We also refer to your March 8, 2012 submission, containing your response to our request for information dated February 23, 2012.

We have the following comments and information request. We request a written response by April 12, 2012, in order to continue our evaluation of your NDA.

1. In your March 8, 2012 response, you did not provide the dissolution "profiles" for the lower strength MS-8 except for the percentage dissolved (one point only) at 30 minutes for 4 batches (see Table 5, page 6 of 8). The dissolution profile data for MS-8 are needed in order to grant your biowaiver for this lower strength. Please submit the dissolution profiles for the lower strength MS-8 and the similarity f2 values comparing the dissolution profiles of MS-8 (test) versus MS-16 (reference).

If you have any questions, call Jagjit Grewal, Regulatory Project Manager, at (301) 796-0846.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology and Inborn
Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

BRIAN K STRONGIN
03/30/2012

Grewal, Jagjit

From: Grewal, Jagjit
Sent: Friday, March 30, 2012 3:44 PM
To: 'Glen Park'
Cc: Grewal, Jagjit
Subject: NDA 022175 Pertzye (pancrelipase) - FDA proposed PI label revisions

Importance: High

Attachments: NDA 022175 Pertzye - FDA proposed PI Revisions 3-30-12.doc

Hello Glen,

Reference is made to your New Drug Application submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Pertzye (pancrelipase) Delayed Release Capsules.

Attached is an annotated WORD document containing FDA's revisions to your proposed package insert label. Please review the noted changes and respond with your acceptance and/or proposed changes by Friday, April 6, 2012.

Additionally, please acknowledge receipt of this correspondence. I can be reached at the below phone number or via email with any questions.



NDA 022175
ertzye - FDA propo.

Jagjit Grewal, M.P.H.
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/OND/ODE III
Food & Drug Administration

Phone: (301) 796-0846 || Fax: (301) 796-9905
Email: Jagjit.Grewal@fda.hhs.gov

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/s/

JAGJIT S GREWAL
03/30/2012



NDA 022175

INFORMATION REQUEST

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

Dear Dr. Sipos:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pertzye (pancrelipase) Delayed-Release Capsules.

We also refer to your November 18, 2011 NDA resubmission in response to our Complete Response action letter dated January 27, 2011.

We are reviewing the chemistry section of your submission and have the following comments and information request. We request a prompt written response in order to continue our evaluation of your NDA.

1. We have reviewed section 3.2.P.1.2 of your submission and request further clarification regarding the proposed label strengths and specifications for the MS-8 and MS-16 drug products enzyme activities. We note that your proposed strengths for amylase and protease are a result of (b) (4) and this calculation was made for both the MS-16 and MS-8 strengths. (b) (4)
(b) (4) is not compliant with 21 CFR 201.51(g) (see tables 3.2.P.1.2.2 and 3.2.P.1.2.3). The potency values for amylase and protease should reflect the actual content of the capsule. Please revise the label claim for amylase and protease appropriately, and update all drug product release and stability results to include the actual potency values, in addition to percentages. Furthermore, please revise your package insert and carton and container labels to reflect the appropriate enzyme activity.

If you have any questions, call Jagjit Grewal, Regulatory Project Manager, at (301) 796-0846.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology and Inborn
Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

BRIAN K STRONGIN
03/29/2012



NDA 022175

INFORMATION REQUEST

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

Dear Dr. Sipos:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pertzye (pancrelipase) Delayed-Release Capsules.

We also refer to your November 18, 2011 NDA resubmission containing your proposed draft carton and container labeling.

We are reviewing the referenced material and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. We note that the proprietary name is presented in all capital letters (i.e. PERTZYE) which decrease readability. Revise the proprietary name to appear in title case (i.e. Pertzye). Words set in upper and lower case form recognizable shapes, making them easier to read than the rectangular shape that is formed by words set in all capital letters.
2. In accordance with 21 CFR 201.10(g)(2), ensure that the established name is printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Additionally, revise the dosage form presentation to be commensurate with the established name presentation.
3. We recommend enlarging the middle portion of the NDC numbers corresponding to the two different strengths of the product. Since this product is available in two (b) (4) different strengths with very similar NDC numbers, and pharmacists normally rely on the middle portion of the NDC number as part of their checking system, highlighting the middle portion of the NDC numbers by enlarging these numbers can help distinguish the two similar NDC numbers, making them less prone to mix-ups by the pharmacy staff.

4. The 100 count and 250 count bottles can be (b) (4) Ensure these bottles utilize child-resistant closures to comply with the Poison Prevention Packaging Act of 1970. As currently described, the closure system is a ‘white (b) (4) screw cap with (b) (4) aluminum liner and induction safety seal.’
5. In accordance with 21 CFR 201.10(d)(1), ensure that any statement of the quantity of an ingredient expresses that quantity of the ingredient in each capsule. The statement and the revised presentation of the ingredients and the quantity of each in each capsule may appear as follows:

Each enteric-coated delayed-release capsule contains:

Dose By Lipase Units	Lipase	X USP Units
	Protease	X USP Units
	Amylase	X USP Units

6. Revise the warning statement (b) (4) that is currently on the side panel of the container labels and carton labeling to read “Pertzye capsules should be swallowed whole. Do not crush or chew the capsules and the capsule contents.” As currently presented, the warning statement contains negative language which may be overlooked by patients and have the opposite effect of the intended meaning. Additionally, ensure the statement is prominent by bolding the statement.
7. Reduce the prominence of the company logo on the principal display panel of the container labels and carton labeling. As currently presented, the company logo appears too large and can distract from important information such as the product strength.

If you have any questions, call Jagjit Grewal, Regulatory Project Manager, at (301) 796-0846.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology and Inborn
Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

BRIAN K STRONGIN
02/24/2012



NDA 022175

INFORMATION REQUEST

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

Dear Dr. Sipos:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pertzye (pancrelipase) Delayed-Release Capsules.

We also refer to your November 18, 2011 NDA resubmission in response to our Complete Response action letter dated January 27, 2011. Additional reference is made to the telecon between representatives of your firm and the FDA on February 22, 2012.

Per discussion at the teleconference, we have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Please correct the lipase activity using the proposed mean correction factor (1.34) and resubmit the complete dissolution data previously requested, i.e., the percent of lipase dissolved at 10, 20, 30, 40, 50 and 60 min (mean and individual, n=6, preferably n=12), and the mean profiles for the MS-8 and MS-16 clinical and stability batches. Also, include your proposal for the dissolution acceptance criterion for lipase for your Pertzye drug product.

If you have any questions, call Jagjit Grewal, Regulatory Project Manager, at (301) 796-0846.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology and Inborn
Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

BRIAN K STRONGIN
02/23/2012

Grewal, Jagjit

From: Grewal, Jagjit
Sent: Tuesday, February 21, 2012 5:21 PM
To: 'Glen Park'
Cc: Grewal, Jagjit
Subject: NDA 022175 Pertzye (pancrelipase) - Request for information

Attachments: NDA 022175 - Request for Information 2-21-12.pdf

Hello Glen,

Reference is made to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pertzye (pancrelipase) Delayed-Release Capsules. We also refer to your November 18, 2011 NDA resubmission in response to our Complete Response action letter dated January 27, 2011.

We have the attached request for additional information. As noted, please provide a response by March 8, 2012.

Please acknowledge receipt of this correspondence. I can be reached via email or at the below phone number with any questions.



NDA 022175 -
Request for Infor...

Jagjit Grewal, M.P.H.
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/OND/ODE III
Food & Drug Administration

Phone: (301) 796-0846 || Fax: (301) 796-9905
Email: Jagjit.Grewal@fda.hhs.gov

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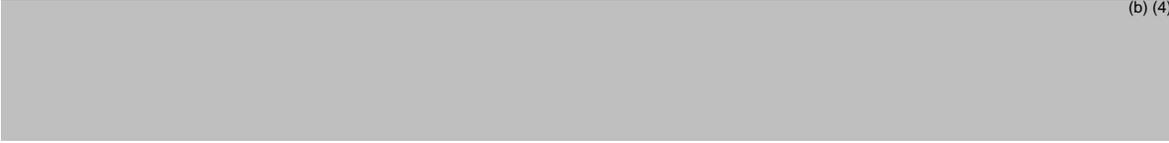
Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We note in your submission, dated June 29, 2009, you requested a partial waiver of pediatric studies in pediatric patients, birth to 1 month of age because the “necessary studies would be impossible or highly impractical.” Once we have reviewed your request, we will notify you if the partial waiver request is denied.

In your resubmission, dated November 18, 2011, you state that the pediatric requirement for pediatric patients 1 month to 1 year is not fulfilled due to the lack of an age appropriate formulation. Please note that PREA requires the development of an age appropriate formulation for **all** relevant pediatric populations unless you can demonstrate that reasonable attempts to produce a pediatric formulation have failed. Before a PREA study requirement can be granted a waiver due to the inability to develop a pediatric formulation, you must submit documentation detailing why a pediatric formulation cannot be developed and the submission detailing the inability to develop the formulation will be promptly posted on the FDA web site. We would consider a deferral for the development of an age appropriate formulation to allow for dosing of the youngest, lowest weight pediatric patients, including infants less than 12 months of age who will be administered 2,000 to 4,000 lipase units per 120 mL of formula or per breast-feeding. All deferral requests must include the justification of the deferral request supporting information and documentation to support the deferral request. You must provide the time frame, i.e. day, month and year, for submission of the data to support marketing of the age appropriate formulation. Please submit the required supporting information and documentation for your partial deferral request. Once we have received the additional data, we will review your request, and we will notify you if the partial deferral request is denied. Of note, you also must provide documentation adequate to support the safety, efficacy and dosing in patients greater than 1 month to less than 1 year (see below).

We note in your November 18, 2011, submission that you state that the pediatric study requirement for pediatric patients 1 year to 17 years of age has been fulfilled. Although additional clinical studies may not be required in patients greater than **1 month** to less than 17 years, PREA requires documentation adequate to assess the safety and effectiveness of the product and adequate to support dosing and administration of the product for each relevant pediatric subpopulation. You must provide documentation to support that the clinical trial data submitted with your NDA, the clinical experience with pancreatic enzyme replacement products in pediatric patients and the body of literature supporting use of the pancreatic enzyme replacement products in pediatric patients are adequate to support the safety, efficacy and dosing of Pertzye in patients 1 month to 17 years.

(b) (4)



Please submit your response by March 8, 2012.

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/s/

JAGJIT S GREWAL
03/07/2012

Grewal, Jagjit

From: Grewal, Jagjit
Sent: Friday, February 17, 2012 4:55 PM
To: 'Glen Park'
Cc: Grewal, Jagjit; 'tsipos@digestivecare.com'
Subject: NDA 022175 Pertzye (pancrelipase) - requests for information/Tcon discussion

Importance: High

Attachments: N22175 Pertzye (pancrelipase) - FDA information requests 2-17-12.doc

Hello Glen,

Reference is made to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pertzye (pancrelipase) Delayed-Release Capsules. We also refer to the teleconference between FDA and Digestive Care, Inc scheduled for Wednesday, February 22, 2012.

Attached are additional FDA comments and requests for information in preparation for the scheduled teleconference discussion.

Please confirm receipt of this correspondence. I can be reached via email or at the below phone number with any questions.



N22175 Pertzye
(pancrelipase) ...

Jagjit Grewal, M.P.H.
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/OND/ODE III
Food & Drug Administration

Phone: (301) 796-0846 || Fax: (301) 796-9905
Email: Jagjit.Grewal@fda.hhs.gov

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1. We acknowledge your February 7, 2012 response to the Agency's request for information dated January 20, 2012. In the response, you indicated that the lipase activity obtained from two methods could be different. The TM-6013 method was performed (b) (4) and the dissolution method was conducted at 37°C (TM-6007 method). We are concerned that the difference could be due to the different temperatures under which the lipase activity was obtained (b) (4) versus 37°C). After reviewing your response, we have the following requests for additional information:
 - a. Submit the recalculated lipase activity (according to USP) using the correction factor allowed for comparisons.
 - b. Clarify if the correction factor is needed for lipase activity only, but not for protease or amylase activity (b) (4). Also, provide an explanation.
2. We are reviewing the manufacturing process validation information you provided, and request the following information to complete our review of the Master Process Validation Summary Report PVR-003.
 - a. Provide the following information in a summary table format for all lots manufactured for the process validation study:
 - i. The pre-defined critical process operating and performance parameters and the actual values that were achieved for each step of the manufacturing process.
 - ii. The results of all in process testing for each step of the manufacturing process.
 - iii. The final release testing results for all process validation lots.
 - b. In support of the Validation Summary Report PVR-003, provide the following:
 - i. The Quality Assurance approved process validation protocol.
 - ii. The complete results of the process validation study (e.g. batch records), for all validation lots.
 - iii. The executed batch production record(s) for all clinical lot(s).
 - iv. A list or table containing a summary of all significant process changes that have occurred since the manufacture of the clinical lot(s).
3. Provide any additional stability results for Pertzye obtained after your November 18, 2011 NDA re-submission.

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/s/

JAGJIT S GREWAL
02/17/2012



NDA 022175

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Digestive Care, Inc.
1120 Win Drive
Bethlehem, Pennsylvania 18017-7049

ATTENTION: Tibor Sipos, Ph.D.
President and Chief Scientific Officer

Dear Dr. Sipos:

Please refer to your New Drug Application (NDA) dated October 27, 2008, received October 27, 2008, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Pancrelipase Delayed-release Capsules.

We also refer to

- the action letter issued by the Division of Gastroenterology and Inborn Errors Products on January 27, 2011;
- your November 18, 2011, resubmission, received November 18, 2011, which included a request for review of your proposed proprietary name, Pertzye;
- the correspondence issued by the Division of Gastroenterology and Inborn Errors Products on December 2, 2011, acknowledging your resubmission as a Complete Response to their January 27, 2011 action letter.

We have completed our review of the proposed proprietary name, Pertzye and have concluded that it is acceptable.

The proposed proprietary name, Pertzye will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your November 18, 2011 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Nitin M. Patel, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5412. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Jagjit Grewal at (301) 796-0846

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
02/10/2012



NDA 022175

INFORMATION REQUEST

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

Dear Dr. Sipos:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pertzye (pancrelipase) Delayed-Release Capsules.

We also refer to your November 18, 2011 NDA resubmission in response to our Complete Response action letter dated January 27, 2011.

We are reviewing the clinical and clinical pharmacology sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Please refer to deficiency #8 identified in the Complete Response letter dated January 27, 2011. It was noted that the validation reports for the lipase (TMV-047) and protease (TMV-043) assay methods submitted on February 15, 2010, were not acceptable to fulfill clinical pharmacology deficiency #19 in the Complete Response letter dated August 27, 2009. In your current resubmission, we have identified reports to address the deficiency noted in the lipase assay validation report, but have not identified a report to address the protease assay validation. If submitted as part of your resubmission, provide the location of the revised protease assay validation report (i.e., module and section).

2.

 (b) (4)

Your response should include an explanation of how the youngest children would receive appropriate dosing with the available dose strengths (MS-8 and MS-16).

If you have any questions, call Jagjit Grewal, Regulatory Project Manager, at (301) 796-0846.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology and Inborn
Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

BRIAN K STRONGIN
01/31/2012



NDA 022175

INFORMATION REQUEST

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

Dear Dr. Sipos:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pertzye (pancrelipase) Delayed-Release Capsules.

We also refer to your November 18, 2011 NDA resubmission in response to our Complete Response action letter dated January 27, 2011.

We acknowledge that your NDA resubmission included some dissolution data. However, these data do not provide the complete dissolution profiles (lipase activity) for your product.

Our review of your Report Number RR-231 (Module 32P53) is briefly summarized below.

Lipase Activity Determination: Three lots of finished products

I. Label Claim: Assay Method (TM-6013)

(b) (4)

II. Label Claim: Dissolution Method (TM-6007) + Assay Method (TM-6013)

(b) (4)

III. Stability Test: Assay Method (TM-6013)

(b) (4)

IV. Stability Test: Dissolution Method (TM-6007) + Assay Method (TM-6013)

(b) (4)

Proposed Acceptance Criterion: $Q =$ (b) (4) at 30 minutes for Lipase Activity

In review of these data, we have the following concerns:

- We are uncertain if the dissolution medium (i.e., fortified intestinal fluid added with 40 mL of olive oil substrate, 40 mL of casein substrate, and 160 mL of 1.00% starch substrate) affects the complete recovery of the lipase activity during the dissolution testing.
- We question if lipase may not be released fast enough from the enteric coating during the time of the dissolution testing (b) (4)
- We are concerned that your proposed acceptance criterion of $Q =$ (b) (4) at 30 minutes for lipase activity is not meaningful, because it will not control the quality of your proposed pancrelipase product.

To address our concerns, we request that you provide the information below. We request a prompt written response in order to continue our evaluation of your NDA.

1. According to Method No. TM-6007, intestinal fluid samples are to be removed for enzyme assay at 10, 20, and 30 min, but only the lipase activity at 30 min was reported. Please provide the complete dissolution data [individual (n=6, preferably n=12, and profiles) at 10, 20, 30, 40, 50, 60 min, etc. until complete dissolution occurs or a plateau is reached]. If incomplete dissolution occurs, please provide mass balance information accounting for 100% of lipase.
2. Please indicate at what pH the enteric coating is designed to dissolve (e.g., pH 5, 5.5, or 6).
3. We noted that you provided the amylase and protease activities (b) (4) for MS-16 and MS-8 (clinical and stability batches; M23P5, pp. 23 and 24 of 35). It is critical for us to know if during the dissolution testing there is the same trend of low recovery/slow release from the microsphere for both amylase and protease. For the dissolution test, please also provide the amylase and protease activity data at 10, 20, 30, 40, 50, and 60 min (individual, mean, and plots). If incomplete dissolution occurs, please provide mass balance information accounting for 100% of amylase and protease.

If you have any questions, call Jagjit Grewal, Regulatory Project Manager, at (301) 796-0846.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology and Inborn
Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

BRIAN K STRONGIN
01/20/2012



NDA 022175

**ACKNOWLEDGE –
CLASS 2 RESPONSE**

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

Dear Dr. Sipos:

We acknowledge receipt on November 18, 2011, of your November 18, 2011, resubmission of your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Pertzye (pancrelipase) Delayed-Release Capsules.

We consider this a complete, class 2 response to our January 27, 2011, action letter. Therefore, the user fee goal date is May 18, 2012.

If you have any questions, call me at (301) 796-0846.

Sincerely,

{See appended electronic signature page}

Jagjit Grewal, M.P.H.
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn
Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

JAGJIT S GREWAL
12/02/2011



NDA 022175

INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

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

Dear Applicant:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pertzye (pancrelipase) Delayed-Release Capsules.

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by Cetero Research in Houston, Texas (Cetero).¹ The pervasiveness and egregious nature of the violative practices by Cetero has led FDA to have significant concerns that the bioanalytical data generated at Cetero from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or “prep” run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or “prep” runs that prevented Cetero and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by Cetero Research in Houston, Texas during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is searching available documentation to determine which NDAs are impacted by the above findings.

¹ These violations include studies conducted by Bioassay Laboratories and BA Research International specific to the Houston, Texas facility.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by Cetero Research in Houston, Texas during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have any questions, call Jagjit Grewal, Regulatory Project Manager, at (301) 796-0846.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn
Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

GIUSEPPE RANDAZZO

09/15/2011

Signed for Dr. Donna Griebel



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type A
Meeting Category: End of Review Meeting

Meeting Date and Time: June 22, 2011; 1:00PM – 2:00PM EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room 1419
Silver Spring, Maryland 20903

Application Number: NDA 022175
Product Name: Pertzye (pancrelipase) Delayed-Release Capsules
Indication: Treatment of exocrine pancreatic insufficiency due to
cystic fibrosis or other conditions

Sponsor/Applicant Name: Digestive Care, Inc.

Meeting Chair: Anil Rajpal, M.D.
Meeting Recorder: Jagjit Grewal, M.P.H

FDA ATTENDEES

Office of Drug Evaluation III

Julie Beitz, M.D. Director

Division of Gastroenterology and Inborn Errors Products

Donna Griebel, M.D. Director
Andrew Mulberg, M.D. Deputy Director
Joyce Korvick, M.D., M.P.H. Deputy Director for Safety
Anil Rajpal, M.D. Medical Team Leader
Marjorie Dannis, M.D. Medical Reviewer
Sushanta Chakder, Ph.D. Pharmacology Team Leader
Brian Strongin, R.Ph., M.B.A. Chief, Project Management Staff
Jagjit Grewal, M.P.H. Senior Regulatory Health Project Manager

Office of Biotechnology Products/Division of Therapeutic Proteins

Emanuela Lacana, Ph.D. Associate Chief, Lab of Chemistry
Howard Anderson, Ph.D. Chemistry Reviewer

Office of Clinical Pharmacology/Division of Clinical Pharmacology III

Yow-Ming Wang, Ph.D. Team Leader

Office of New Drug Quality Assessment

Tien Mien Chen, Ph.D. Biopharmaceutics Reviewer

Office of Pharmaceutical Science/New Drug Microbiology Staff

Vinayak Pawar, Ph.D. Microbiology Reviewer

Office of Compliance/Division of Manufacturing and Product Quality

Francis Godwin Compliance Officer

SPONSOR ATTENDEES

Digestive Care, Inc.

Tibor Sipos, Ph.D.	President and Chief Scientific Officer
Steve Berens	Vice President, Sales and Marketing
Frank Manella	Quality System Director
Robin LaPadula	Project Coordinator

Target Health, Inc.

Glen Park, Pharm.D. Senior Director, Clinical/Regulatory Affairs

(b) (4)

1.0 BACKGROUND

Reference is made to NDA 022175 Pertzye (pancrelipase) delayed-release capsules, dated October 27, 2008. FDA issued a Complete Response letter on January 27, 2011 noting product quality, clinical pharmacology, and facility inspection deficiencies. Among the specific deficiencies listed was an inadequate manufacturing facility inspection for the drug substance supplier (b) (4) unacceptable retrospective validation reports for the drug product manufacturing process, unacceptable real-time stability data to support the proposed expiry period, requests for additional information on release and stability requirements, and an unacceptable applesauce compatibility study report.

Digestive Care, Inc. (DCI) submitted a Type A End of Review meeting request, dated May 2, 2011, to discuss the deficiencies outlined in the January 27, 2011 Complete Response letter and obtain FDA feedback on requirements to support NDA resubmission.

FDA granted DCI's meeting request in the letter dated May 16, 2011. The sponsor's meeting background package was received on June 7, 2011. FDA preliminary comments were sent to the sponsor on June 17, 2011. On June 21, 2011, DCI provided responses to the FDA preliminary comments for discussion at the meeting.

In their background package, DCI noted that their development program has stalled due to ongoing issues regarding the acceptability of (b) (4) as an approvable supplier of the pancrelipase API. As a back-up strategy, DCI proposed that pancrelipase API from an alternative supplier, (b) (4) be allowed as a substitute. The sponsor explained that (b) (4) has supplied the API for two of the currently approved pancrelipase products. Additionally, DCI stated that substitution of the API suppliers can be justified by the analytical characterization including RP-HPLC and SDS-PAGE profiles of protein constituents, the same drug product formulation and manufacturing process being used, enzyme content ratios within that of other approved PEPs, and both APIs have been used in clinical studies demonstrating safety and effectiveness.

(b) (4)

2.0 DISCUSSION

The format of these minutes provides for DCI's questions in regular typeface, followed by the FDA's June 17, 2011 responses in **bolded** print. DCI's June 21, 2011 replies to the FDA responses are presented in *italic* print. The June 22, 2011 meeting discussion is presented in *italic and bolded* print.

Question #1a: Has (b) (4) sufficiently addressed all the DMF deficiencies, except for the BDE item?

FDA Response:

FDA communicated product manufacturing issues to (b) (4) in a letter dated October 27, 2010. If (b) (4) has addressed in full the product issues listed in the letter, FDA will review (b) (4) responses once an NDA referencing the (b) (4) DMF is resubmitted. At the time of resubmission, you should communicate to the Agency that the DMF holder has addressed all the deficiencies and ensure that (b) (4) provides the Agency with references to the submission(s) where the deficiencies are addressed.

DCI Comments: (b) (4) submitted a response to the October 27, 2010 DMF deficiency letter to FDA on November 8, 2010. In a letter dated November 10, 2010, DCI notified the FDA that the (b) (4) DMF response was submitted in support of the DCI NDA. Was the November 8, 2010 (b) (4) response to the October 27, 2010

DMF deficiency letter reviewed by the FDA prior to the issuance of DCI's CR letter dated January 27, 2011?

Meeting Discussion:

(b) (4) should update the DMF to include any corrections from the (b) (4) (b) (4) should notify the project manager when the DMF is updated. (b) (4) should indicate if previous responses addressed outstanding deficiencies and where the information is specifically located.

FDA cannot review the DMF until the NDA is resubmitted. DCI requested FDA to consider reviewing the DMF information prior to NDA resubmission. FDA will consider the request based on available resources.

Question #1b: Would the Agency accept DCI's NDA resubmission and allow (b) (4), to complete the BDE method development work and implementation of the validated test during the DCI NDA review and/or as a post approval commitment?

FDA Response:

To resolve the BDE issue, (b) (4) should officially submit all the information showing that the currently available BDE assay is not suited for the purpose of detecting BDE in pancrelipase and showing that appropriate in-process controls are in place that limit BDE production during manufacturing.

DCI Comments: We are requesting further discussion/clarification on this topic during the meeting.

Meeting Discussion:

See the discussion for question #1a.

FDA clarified that in-process controls refers to reducing and controlling microbial count.

FDA referred DCI to the Biologics Price Competition and Innovation Act and noted that protein products currently under NDAs would be transitioned to BLAs in approximately 10 years. FDA recommends that DCI review the provisions of the law.

Question #2a: Is (b) (4) an FDA approvable supplier of the pancrelipase API within the next 3-6 months?

FDA Response:

(b) (4) compliance status is being re-evaluated at this time. We suggest that you contact (b) (4) for additional information.

DCI Comments: DCI has learned from (b) (4) that the FDA completed a re-inspection of the (b) (4) facilities on June 17, 2011 with no Form FDA-483 issued at the conclusion. Given the results of the recently completed inspection, is (b) (4) now considered to be approvable as a supplier of pancrelipase to DCI's NDA?

Meeting Discussion:

FDA recommended DCI to stay in contact with (b) (4) and ask for notification when the close out letter is issued. FDA noted that when the NDA is resubmitted, additional pre-approval inspections may be required.

Question #2b: Should DCI proceed with the drug product PV plan using the (b) (4) or the (b) (4) API?

FDA Response:

The 2006 FDA Guidance for Industry Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs states, “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.” If you decide to use (b) (4) as a source of pancrelipase drug substance, you will need to conduct a clinical trial using drug product manufactured with the (b) (4) API. Please also refer to the FDA written communications to DCI dated 11/2/09 (for NDA 22175) and 11/6/2007 (for IND 45223).

DCI Comments: No further questions at this time.

Question #2c: Would the Agency accept DCI's NDA resubmission based on a commitment from DCI to complete the PV during the NDA review and/or prior to commercialization?

FDA Response:

No. Pancrelipase products are complex biological products. Process validation should be completed to demonstrate the ability to consistently manufacture Pertzye, and the study is required to support approval of the NDA. The process validation final study report should be included in the resubmission.

DCI Comments: As requested by the Agency, DCI fully intends to execute a prospective process validation (PV). The PV master plan (PV-003) was provided to the Agency during the on-site facility inspections, and within the prior NDA resubmission dated February 15, 2010. A copy of PV-003 was provided in Attachment 9 of the briefing document for ease of reference. Can FDA acknowledge agreement with PV-003 before DCI commits the resources to

complete the PV, and to enable commercialization of the PV batches post-approval, including the use of current inventories of (b) (4) API?

Meeting Discussion:

FDA noted that the PV plan appeared adequate upon initial review, but a final determination will be made upon review of the PV summary report.

DCI indicated that they have current inventory of (b) (4) API, and asked if this can be commercialized. FDA recommended that DCI contact (b) (4) for additional information on the lots and conduct analyses (in-process controls) to determine if the lots are acceptable. DCI should ensure that the (b) (4) API lots that are currently in house at DCI were manufactured using the current manufacturing process described in the DMF. (b) (4) should include a summary of the changes that have occurred from the clinical lot.

FDA Post-Meeting Comments:

Regarding (b) (4) API lots currently in DCI's Inventory, FDA recommends that prior to use in manufacturing of to be commercialized product, DCI conduct a thorough quality review of the lots in question to assure that they meet all appropriate specifications and standards of identity, strength, quality and purity. DCI may have to contact (b) (4) to facilitate this review. Issues of concern are in-process controls as well as issues identified in the FDA Warning Letter issued to (b) (4). Specifically, the potential presence of (b) (4) in the API material should be addressed as part of the review.

Question #3: Would the Agency consider allowing DCI to gather additional information to establish the upper limit for protease and amylase in the pancrelipase API, as a postmarketing commitment?

FDA Response:

No. The resubmission should include provisional specifications, established upon your manufacturing history and capability, and clinical experience. For additional guidance on establishing specifications, please refer to ICH Q6B. As a post-marketing commitment, acceptance criteria can be revised once a sufficient number of lots has been manufactured.

DCI Comments: No further questions at this time

Question #4: Would the Agency consider that real time stability data on one lot of (b) (4) (MS-8) are sufficient to support assignment of an expiry date (to be based on real time data available at the time of resubmission) for those strengths?

FDA Response:

No. In order to determine expiry, a minimum of six months stability data on three lots of commercial material should be included in the resubmission, along with stability data on lots representative of the commercial manufacturing process.

DCI Comments: At this time, DCI intends to limit the NDA resubmission to the MS-16 and MS-8 strengths. At the time of NDA resubmission, real time stability data will be available for at least 3 lots of MS-8 and MS-16 (one is the pivotal clinical study batch), all with greater than 18 months of data. All lots are representative of the TbMP commercial manufacturing process and filled at 100% label claim lipase activity. Please clarify if this meets the requirement for "commercial material" along with "lots representative of the commercial manufacturing process".

Meeting Discussion:

DCI corrected an error in the background package and stated that there are 3 lots, not 1, of MS-8. FDA asked DCI to provide historical stability data on lots manufactured using the same process as the to be marketed product. FDA requested DCI to provide trending charts for critical attributes and to specify the proposed expiration date of the drug product.

Question #5: Please confirm that the Agency indeed was referring to the "drug product" reference standard for this item.

FDA Response:

Yes. This CR item refers to the drug product.

DCI Comments: No further questions at this time.

Question #6: DCI is seeking clarification from the Agency on the requirement for incorporating accelerated and/or stressed stability studies in the routine annual stability program for the drug product.

FDA Response:

As stated above, the purpose of the annual stability evaluation is to both confirm expiry as well as to confirm product quality. Accelerated stability evaluation or stress studies are usually conducted in the evaluation of product physico-chemical comparability since they are sensitive to detect changes in product quality attributes. In any given year, there are multiple "operational changes" that occur as required by manufacturing operations. In-process and release testing may not detect small changes in product attributes. The FDA feels that for protein products the annual stability program should include the evaluation of at least one lot at accelerated conditions for the continued confirmation of product quality. The data

obtained in these studies should be trended and evaluated against the historical data generated under the same conditions. Your protocol should also include a description of how results that do not fall within historical trends will be evaluated and used to provide better assurance of product quality.

DCI Comments: No further questions at this time.

Question #7a: Would the Agency accept DCI's NDA resubmission containing the information described above; and, in order to allow additional experience to be gained on the TbMP to enable setting of a meaningful specification, would the Agency consider allowing DCI to establish the final RP-HPLC specifications for release and shelf-life as a post-approval commitment?

FDA Response:

No. The resubmission should include provisional specifications, established upon your history and capability, and clinical experience. For additional guidance on establishing specifications, please refer to ICH Q6B. As a post-marketing commitment, acceptance criteria can be revised once a sufficient number of lots has been manufactured.

DCI Comments: No further questions at this time.

Question #7b: DCI's proposed acceptance criteria are based on the results obtained on real time data on NDA stability lots and the clinical lot. Given that the Agency has reviewed and approved 3 PEP drug products, DCI is seeking guidance from the Agency on the best manner in which to establish a meaningful specification for HPLC (e.g., number of lots, acceptable band width, etc.).

FDA Response:

We recommend that you follow ICH Q6B for setting specifications. Standard approaches could be used for measuring peaks (for example, area under the curve); if necessary, you should plan on requesting the advice of appropriate consultant companies.

DCI Comments: No further questions at this time.

Question #8a: DCI is requesting clarification as to the applicability of the Guidance for Industry: Bioanalytical Method Validation referenced by the Agency, to the applesauce study which is an in vitro testing system.

FDA Response:

The Guidance for Industry: Bioanalytical Method Validation pertains to the analysis of drug samples in a (b) (4). The testing being performed consists of the analysis of pancrelipase in applesauce which is a (b) (4) and therefore the same principles of methodology and validation apply.

DCI Comments: DCI does not comprehend assignment of applesauce as a (b) (4) within the context of these in vitro stability studies. The applesauce is a vehicle for delivery of the microspheres. During the in vitro stability studies performed to support this manner of administration, the microspheres were mixed with the applesauce for the specified amount of time. The applesauce is then rinsed off the microspheres. The recovered microspheres are then tested in the same manner as product release/stability testing for total lipase activity. Applesauce is not included in the lipase activity determination test system. The lipase assay is a USP test method, and was verified accordingly as documented in the reports submitted in the NDA. The lipase assay is run simultaneously with the USP lipase reference standard.

Given that resolution cannot be obtained to the items listed herein under #8, DCI may need to forego including instructions for administration in applesauce in the product labeling. Further discussion of this topic is requested during the meeting, only if time permits.

Meeting Discussion:

FDA referred DCI to section 5B of the noted guidance for the characterization of recovery from the applesauce mixture. DCI should demonstrate recovery post wash and over 3 independent runs, for example 3 different days. The inter-day precision and accuracy should be demonstrated in the validation report.

Question #8b: DCI is requesting a more detailed explanation as to why the analytical method validation reports for the lipase (TMV-047) and protease (TMV-043) assay methods with the 5-point linearity determination, submitted on February 15, 2010, are not acceptable to fulfill Clinical Pharmacology Deficiency #19 requirements.

FDA Response:

This information previously provided was reviewed in the previous review cycle and the deficiencies noted in the Complete Response letter dated January 27, 2011.

The improved assay method is not acceptable to determine the product compatibility. Although the applicant addressed the issue on constructing calibration curves for lipase and protease assay methods (CMC Deficiency #10), the applicant did not determine the accuracy and precision of the assay methods by simultaneously running quality control (QC) samples to check in-process pancrelipase assay performance.

We recommend that you refer to the Guidance for Industry: Bioanalytical Method Validation for more details on the assessment of specificity, accuracy and precision of the assay methods. As an example, the in-process assay performance during actual study sample runs should be determined; the between-assay variability should be assessed but could not be achieved with the submitted data which contain only one validation run with calibration curves.

DCI Comments: See comments in 8a above.

Question #8c:

(b) (4)

(b) (4) For the administration of the drug product microspheres in applesauce, the desired number of capsules is opened and the contents mixed with the applesauce. Therefore, the product strength is irrelevant in this regard. DCI is requesting clarification as to the rationale for performing the same experiments using each (b) (4) drug product strengths.

FDA Response:

If the drug product microspheres in the

(b) (4)

then it is not necessary to perform the food compatibility study using each (b) (4) drug product strengths; however, as stated in the January 27, 2011 CR Letter, you will be required to test at least three product batches.

DCI Comments: See comments in 8a above.

Question #8d: DCI is requesting clarification as to the need for repeating the applesauce study, given that the validated lipase assay was used to test a total of 5 lots of encapsulated microspheres (b) (4) and the results confirm that the microspheres are stable in applesauce for up to 20 minutes.

FDA Response:

The compatibility data you submitted is not sufficient to determine whether it is compatible to mix the proposed product with apple sauce. As mentioned in the response to Question 8b, you did not adequately validate the pancrelipase assay methods and did not submit data on the in-process assay performance. Furthermore, the compatibility study report (RR-166) that you submitted does not contain sufficient information for review. We recommend that you refer to the Guidance for Industry: Bioanalytical Method Validation for more details on the application of validated method to routine drug analysis.

DCI Comments: See comments in 8a above.

Question #9a: Would substitution of the (b) (4) pancrelipase API with the (b) (4) API in DCI's drug product eliminate FDA concerns associated with the compliance issues identified at (b) (4)?

FDA Response:

See the response to question 2b.

DCI Comments: No further questions at this time.

Question #9b: Would substitution of the (b) (4) pancrelipase API with the (b) (4) API in DCI's drug product eliminate FDA concerns associated with the issues identified in the (b) (4) DMF?

FDA Response:

See the response to question 2b.

DCI Comments: No further questions at this time.

Question #9c: Could the substitution of the (b) (4) pancrelipase API with the (b) (4) API in DCI's drug product be implemented as part of the resubmission to the current DCI NDA #22-175?

FDA Response:

See the response to question 2b.

DCI Comments: No further questions at this time.

Question #9d: DCI has already demonstrated that its PEP drug product formulation is safe and effective (reference clinical study 06-001). The (b) (4) API has been shown to be safe and effective in 2 currently approved PEP NDAs. The DCI PEP made with the (b) (4)

Therefore, DCI believes that a clinical study would not be required to support the API supplier switch in DCI's drug product formulation. Does the Agency agree?

FDA Response:

No, we do not agree. A clinical study would be required. See the response to question 2b above and the response to question 9f below.

DCI Comments: No further questions at this time.

Question #9e: If a clinical study is not required, what would the criteria be for demonstrating comparability of the DCI PEP made with the (b) (4) API to that made with the (b) (4) API?

FDA Response:

See the response to question 9d.

DCI Comments: No further questions at this time.

Question #9f: If a clinical study is required, what would the criteria be for demonstrating treatment effect (i.e., minimum %CFA difference between active and placebo)?

FDA Response:

A clinical study will be required which utilizes each to-be-marketed (TBM) formulation (i.e., each capsule strength) of the proposed new DCI product (using the (b) (4) drug substance) that has a unique ratio of lipase:amylase:protease or a unique microsphere size. We refer you to the guidance document "Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs" for further information. We also recommend that you include a substantial proportion of patients (i.e., more than 25% of the study population) with baseline CFA < 40%. The change in CFA should be similar to that of the approved PEPs for both the overall study population and the subgroup of patients with baseline CFA < 40%.

In addition to the required clinical trial above, dissolution profiles (plus individual and mean dissolution data; n=12/strength) for each capsule strength of the proposed new DCI product (using the (b) (4) drug substance) should be submitted.

See also the FDA Additional Comments.

DCI Comments: In DCI's pivotal clinical trial (Protocol 06-001), approximately 40% of the patients had a %CFA of <40% while on placebo. Would the same study design as used for Protocol 06-001 be acceptable in the case that DCI would pursue using the (b) (4) drug substance?

Meeting Discussion:

FDA considers the placebo CFA to be representative of the baseline CFA. Further information regarding the approved PEPs is available on the Drugs@FDA website. FDA also referred the sponsor to the January 2011 GIDAC meeting.

FDA Post-Meeting Comments:

See the FDA Post-Meeting Comments under FDA Additional Comment #1 below.

Question #9g: If (b)(4), eventually resolves its deficiencies and becomes an FDA approved supplier of pancrelipase API, would DCI be able to utilize both pancrelipase API manufacturers for our drug product under the same NDA#22-175?

FDA Response:

No. Given that physicochemical similarity of the (b)(4) drug substance and the (b)(4) drug substance cannot be determined based on quality criteria alone, you will be creating different drug products. Thus, these drug products cannot be filed under the same NDA 022175.

DCI Comments: *No further questions at this time.*

Question #10: Does the Agency agree that resubmission of the draft labeling is not required?

FDA Response:

No, we do not agree. A resubmission of the draft labeling will be required.

DCI Comments: *No further questions at this time.*

Question #11: Does the Agency agree that a REMS (including a timetable for assessment) would no longer be required for DCI's NDA?

FDA Response:

Yes, we agree that a REMS will no longer be required for DCI's NDA.

DCI Comments: *No further questions at this time.*

FDA ADDITIONAL COMMENTS:

- 1. Please clarify the size of microspheres to be used in the new DCI product (using the (b)(4) drug substance). You may consider developing a formulation that uses a smaller size of microspheres in the lowest capsule strength, and including that formulation in your pivotal clinical study (oral dosing).**

If you are able to demonstrate efficacy of that capsule strength via oral dosing, then demonstration of successful delivery in an *in vitro* study of direct administration of the contents via a gastrostomy tube (G-tube) will allow you to

include this method of administration in the Dosage and Administration section. Smaller microspheres may be more easily administered via G-tube for feeding to younger patients.

DCI Comments: [REDACTED] (b) (4)

[REDACTED] (b) (4)

We understand that a clinical trial would be required if we use the [REDACTED] (b) (4) API. However, would a clinical trial be needed for the G-tube product as defined above made with the [REDACTED] (b) (4) API?

[REDACTED] (b) (4)

Meeting Discussion:

FDA stated that a clinical trial would be needed for each formulation that has a specific microsphere size range. FDA agreed that [REDACTED] (b) (4)

[REDACTED] would be acceptable as an age-appropriate formulation for pediatric patients.

FDA Post-Meeting Comments:

Based on additional internal discussion that included the clinical review team and the ONDQA biopharmaceutics review team, we have determined that if the dissolution profile of the smaller size microspheres is the same as that of the larger size microspheres, then no additional in vivo (clinical) studies will be required. However, if the release characteristics were found to be different, then additional in vivo studies would be required to rule out any differences in clinical performance.

2. You should address the points outlined in the “Additional Comments” section of the January 27, 2011 Complete Response letter with your NDA resubmission.

DCI Comments: *No further questions at this time.*

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/s/

JAGJIT S GREWAL
07/22/2011



NDA 022175

MEETING PRELIMINARY COMMENTS

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

Dear Dr. Sipos:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pertzye (pancrelipase) Delayed-Release Capsules.

We also refer to your May 2, 2011, correspondence, received May 2, 2011, requesting a meeting to discuss the deficiencies outlined in our Complete Response letter dated January 27, 2011, and the steps to be taken for your NDA resubmission.

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for June 22, 2011 from 1:00-2:00PM EST at FDA's White Oak Campus between Digestive Care, Inc. and the Division of Gastroenterology and Inborn Errors Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting

Question #1a: Has (b) (4) sufficiently addressed all the DMF deficiencies, except for the BDE item?

FDA Response:

FDA communicated product manufacturing issues to (b) (4) in a letter dated October 27, 2010. If (b) (4) has addressed in full the product issues listed in the letter, FDA will review (b) (4) responses once an NDA referencing the (b) (4) DMF is resubmitted. At the time of resubmission, you should communicate to the Agency that the DMF holder has addressed all the deficiencies and ensure that (b) (4) provides the Agency with references to the submission(s) where the deficiencies are addressed.

Question #1b: Would the Agency accept DCI's NDA resubmission and allow (b) (4) to complete the BDE method development work and implementation of the validated test during the DCI NDA review and/or as a post approval commitment?

FDA Response:

To resolve the BDE issue, (b) (4) should officially submit all the information showing that the currently available BDE assay is not suited for the purpose of detecting BDE in pancrelipase and showing that appropriate in-process controls are in place that limit BDE production during manufacturing.

Question #2a: Is (b) (4) an FDA approvable supplier of the pancrelipase API within the next 3-6 months?

FDA Response:

(b) (4) compliance status is being re-evaluated at this time. We suggest that you contact (b) (4) for additional information.

Question #2b: Should DCI proceed with the drug product PV plan using the (b) (4) or the (b) (4) API?

FDA Response:

The 2006 FDA Guidance for Industry Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs states, “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.” If you decide to use (b) (4) as a source of pancrelipase drug substance, you will need to conduct a clinical trial using drug product manufactured with the (b) (4) API. Please also refer to the FDA written communications to DCI dated 11/2/09 (for NDA 22175) and 11/6/2007 (for IND 45223).

Question #2c: Would the Agency accept DCI's NDA resubmission based on a commitment from DCI to complete the PV during the NDA review and/or prior to commercialization?

FDA Response:

No. Pancrelipase products are complex biological products. Process validation should be completed to demonstrate the ability to consistently manufacture Pertzye, and the study is required to support approval of the NDA. The process validation final study report should be included in the resubmission.

Question #3: Would the Agency consider allowing DCI to gather additional information to establish the upper limit for protease and amylase in the pancrelipase API, as a postmarketing commitment?

FDA Response:

No. The resubmission should include provisional specifications, established upon your manufacturing history and capability, and clinical experience. For additional guidance on establishing specifications, please refer to ICH Q6B. As a post-marketing commitment, acceptance criteria can be revised once a sufficient number of lots has been manufactured.

Question #4: Would the Agency consider that real time stability data on one lot of [REDACTED] (b) (4) [REDACTED] MS-8) are sufficient to support assignment of an expiry date (to be based on real time data available at the time of resubmission) for those strengths?

FDA Response:

No. In order to determine expiry, a minimum of six months stability data on three lots of commercial material should be included in the resubmission, along with stability data on lots representative of the commercial manufacturing process.

Question #5: Please confirm that the Agency indeed was referring to the “drug product” reference standard for this item.

FDA Response:

Yes. This CR item refers to the drug product.

Question #6: DCI is seeking clarification from the Agency on the requirement for incorporating accelerated and/or stressed stability studies in the routine annual stability program for the drug product.

FDA Response:

As stated above, the purpose of the annual stability evaluation is to both confirm expiry as well as to confirm product quality. Accelerated stability evaluation or stress studies are usually conducted in the evaluation of product physico-chemical comparability since they are sensitive to detect changes in product quality attributes. In any given year, there are multiple “operational changes” that occur as required by manufacturing operations. In-process and release testing may not detect small changes in product attributes. The FDA feels that for protein products the annual stability program should include the evaluation of at least one lot at accelerated conditions for the continued confirmation of product

quality. The data obtained in these studies should be trended and evaluated against the historical data generated under the same conditions. Your protocol should also include a description of how results that do not fall within historical trends will be evaluated and used to provide better assurance of product quality.

Question #7a: Would the Agency accept DCI's NDA resubmission containing the information described above; and, in order to allow additional experience to be gained on the TbMP to enable setting of a meaningful specification, would the Agency consider allowing DCI to establish the final RP-HPLC specifications for release and shelf-life as a post-approval commitment?

FDA Response:

No. The resubmission should include provisional specifications, established upon your history and capability, and clinical experience. For additional guidance on establishing specifications, please refer to ICH Q6B. As a post-marketing commitment, acceptance criteria can be revised once a sufficient number of lots has been manufactured.

Question #7b: DCI's proposed acceptance criteria are based on the results obtained on real time data on NDA stability lots and the clinical lot. Given that the Agency has reviewed and approved 3 PEP drug products, DCI is seeking guidance from the Agency on the best manner in which to establish a meaningful specification for HPLC (e.g., number of lots, acceptable band width, etc.).

FDA Response:

We recommend that you follow ICH Q6B for setting specifications. Standard approaches could be used for measuring peaks (for example, area under the curve); if necessary, you should plan on requesting the advice of appropriate consultant companies.

Question #8a: DCI is requesting clarification as to the applicability of the Guidance for Industry: Bioanalytical Method Validation referenced by the Agency, to the applesauce study which is an in vitro testing system.

FDA Response:

The Guidance for Industry: Bioanalytical Method Validation pertains to the analysis of drug samples in a (b) (4). The testing being performed consists of the analysis of pancrelipase in applesauce which is a (b) (4), and therefore the same principles of methodology and validation apply.

Question #8b: DCI is requesting a more detailed explanation as to why the analytical method validation reports for the lipase (TMV-047) and protease (TMV-043) assay methods with the 5-point linearity determination, submitted on February 15, 2010, are not acceptable to fulfill Clinical Pharmacology Deficiency #19 requirements.

FDA Response:

This information previously provided was reviewed in the previous review cycle and the deficiencies noted in the Complete Response letter dated January 27, 2011.

The improved assay method is not acceptable to determine the product compatibility. Although the applicant addressed the issue on constructing calibration curves for lipase and protease assay methods (CMC Deficiency #10), the applicant did not determine the accuracy and precision of the assay methods by simultaneously running quality control (QC) samples to check in-process pancrelipase assay performance.

We recommend that you refer to the Guidance for Industry: Bioanalytical Method Validation for more details on the assessment of specificity, accuracy and precision of the assay methods. As an example, the in-process assay performance during actual study sample runs should be determined; the between-assay variability should be assessed but could not be achieved with the submitted data which contain only one validation run with calibration curves.

Question #8c: (b) (4)

(b) (4) For the administration of the drug product microspheres in applesauce, the desired number of capsules is opened and the contents mixed with the applesauce. Therefore, the product strength is irrelevant in this regard. DCI is requesting clarification as to the rationale for performing the same experiments using each of the (b) (4) product strengths.

FDA Response:

If the drug product microspheres in the (b) (4) new MS-8 product strength are (b) (4) then it is not necessary to perform the food compatibility study using each of the (b) (4) drug product strengths; however, as stated in the January 27, 2011 CR Letter, you will be required to test at least three product batches.

Question #8d: DCI is requesting clarification as to the need for repeating the applesauce study, given that the validated lipase assay was used to test a total of 5 lots of encapsulated microspheres (b) (4) and the results confirm that the microspheres are stable in applesauce for up to 20 minutes.

FDA Response:

The compatibility data you submitted is not sufficient to determine whether it is compatible to mix the proposed product with apple sauce. As mentioned in the response to Question 8b, you did not adequately validate the pancrelipase assay methods and did not submit data on the in-process assay performance. Furthermore, the compatibility study report (RR-166) that you submitted does not contain sufficient information for review. We recommend that you refer to the Guidance for Industry: Bioanalytical Method Validation for more details on the application of validated method to routine drug analysis.

Question #9a: Would substitution of the (b) (4) pancrelipase API with the (b) (4) API in DCI's drug product eliminate FDA concerns associated with the compliance issues identified at (b) (4)?

FDA Response:

See the response to question 2b.

Question #9b: Would substitution of the (b) (4) pancrelipase API with the (b) (4) API in DCI's drug product eliminate FDA concerns associated with the issues identified in the (b) (4) DMF?

FDA Response:

See the response to question 2b.

Question #9c: Could the substitution of the (b) (4) pancrelipase API with the (b) (4) API in DCI's drug product be implemented as part of the resubmission to the current DCI NDA #22-175?

FDA Response:

See the response to question 2b.

Question #9d: DCI has already demonstrated that its PEP drug product formulation is safe and effective (reference clinical study 06-001). The (b) (4) API has been shown to be safe and effective in 2 currently approved PEP NDAs. The DCI PEP made with the (b) (4)

Therefore, DCI believes that a clinical study would not be required to support the API supplier switch in DCI's drug product formulation. Does the Agency agree?

FDA Response:

No, we do not agree. A clinical study would be required. See the response to question 2b above and the response to question 9f below.

Question #9e: If a clinical study is not required, what would the criteria be for demonstrating comparability of the DCI PEP made with the (b) (4) API to that made with the (b) (4) API?

FDA Response:

See the response to question 9d.

Question #9f: If a clinical study is required, what would the criteria be for demonstrating treatment effect (i.e., minimum %CFA difference between active and placebo)?

FDA Response:

A clinical study will be required which utilizes each to-be-marketed (TBM) formulation (i.e., each capsule strength) of the proposed new DCI product (using the (b) (4) drug substance) that has a unique ratio of lipase:amylase:protease or a unique microsphere size. We refer you to the guidance document “Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs” for further information. We also recommend that you include a substantial proportion of patients (i.e., more than 25% of the study population) with baseline CFA < 40%. The change in CFA should be similar to that of the approved PEPs for both the overall study population and the subgroup of patients with baseline CFA < 40%.

In addition to the required clinical trial above, dissolution profiles (plus individual and mean dissolution data; n=12/strength) for each capsule strength of the proposed new DCI product (using the (b) (4) drug substance) should be submitted.

See also the FDA Additional Comments.

Question #9g: If (b) (4), eventually resolves its deficiencies and becomes an FDA approved supplier of pancrelipase API, would DCI be able to utilize both pancrelipase API manufacturers for our drug product under the same NDA#22-175?

FDA Response:

No. Given that physicochemical similarity of the (b) (4) drug substance and the (b) (4) drug substance cannot be determined based on quality criteria alone, you will be creating different drug products. Thus, these drug products cannot be filed under the same NDA 022175.

Question #10: Does the Agency agree that resubmission of the draft labeling is not required?

FDA Response:

No, we do not agree. A resubmission of the draft labeling will be required.

Question #11: Does the Agency agree that a REMS (including a timetable for assessment) would no longer be required for DCI’s NDA?

FDA Response:

Yes, we agree that a REMS will no longer be required for DCI’s NDA.

FDA ADDITIONAL COMMENTS:

1. Please clarify the size of microspheres to be used in the new DCI product (using the (b) (4) drug substance). You may consider developing a formulation that uses a smaller size of microspheres in the lowest capsule strength, and including that formulation in your pivotal clinical study (oral dosing).

If you are able to demonstrate efficacy of that capsule strength via oral dosing, then demonstration of successful delivery in an *in vitro* study of direct administration of the contents via a gastrostomy tube (G-tube) will allow you to include this method of administration in the Dosage and Administration section. Smaller microspheres may be more easily administered via G-tube for feeding to younger patients.

- 2. You should address the points outlined in the “Additional Comments” section of the January 27, 2011 Complete Response letter with your NDA resubmission.**

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at (301) 796-0846.

Sincerely,

{See appended electronic signature page}

Jagjit Grewal, M.P.H.
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn
Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

JAGJIT S GREWAL
06/17/2011



NDA 022175

MEETING REQUEST GRANTED

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

Dear Dr. Sipos:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pertzye (pancrelipase) Delayed-Release Capsules.

We also refer to your May 2, 2011 correspondence requesting an End of Review meeting to discuss the deficiencies outlined in our Complete Response letter dated January 27, 2011, and the steps to be taken for your NDA resubmission. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting.

The meeting is scheduled as follows:

Date: June 22, 2011
Time: 1:00-2:00PM EST
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room 1419
Silver Spring, Maryland 20903

Tentative CDER participants:

Office of Drug Evaluation III

Julie Beitz, M.D. Director

Division of Gastroenterology and Inborn Errors Products

Donna Griebel, M.D. Director
Andrew Mulberg, M.D. Deputy Director
Joyce Korvick, M.D., M.P.H. Deputy Director for Safety
Anil Rajpal, M.D. Medical Team Leader
Marjorie Dannis, M.D. Medical Reviewer
Sushanta Chakder, Ph.D. Pharmacology Team Leader
Tamal Chakraborti, Ph.D. Pharmacology Reviewer
Jagjit Grewal, M.P.H. Senior Regulatory Health Project Manager

Division of Therapeutic Proteins

Barry Cherney, Ph.D.	Deputy Director
Gibbes Johnson, Ph.D.	Chief, Lab of Chemistry
Emanuela Lacana, Ph.D.	Associate Chief, Lab of Chemistry
Howard Anderson, Ph.D.	Chemistry Reviewer

Division of Clinical Pharmacology and Biopharmaceutics III

Yow-Ming Wang, Ph.D.	Team Leader
Allen Rudman, Ph.D.	Reviewer

Office of New Drug Quality Assessment

Patrick Marroum, Ph.D.	Special Assistant to the Office Director
Tien Mien Chen, Ph.D.	Biopharmaceutics Reviewer

Office of Pharmaceutical Assessment, New Drug Microbiology Staff

Vinayak Pawar, Ph.D.	Microbiology Reviewer
Stephen Langille, Ph.D.	Microbiology Reviewer

Office of Compliance, Division of Manufacturing and Product Quality

Francis Godwin	Compliance Officer
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Please e-mail me any updates to your attendees at Jagjit.Grewal@fda.hhs.gov, at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is defined as any non-U.S. citizen or dual citizen who does not have a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Jagjit Grewal, (301) 796-0846; Doris Garrison, (301) 796-2120.

Submit background information for the meeting (three paper copies or one electronic copy to the application and 25 desk copies to me) at least two weeks prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by June 8, 2011, we may cancel or reschedule the meeting.

Submit the 25 desk copies to the following address:

If sending via USPS, please send to:

Jagjit Grewal
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room 5109
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

If sending via any carrier other than USPS
(e.g., UPS, DHL), please send to:

Jagjit Grewal
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room 5109
10903 New Hampshire Avenue
Silver Spring, Maryland 20903

If you have any questions, call me at (301) 796-0846.

Sincerely,

{See appended electronic signature page}

Jagjit Grewal, M.P.H.
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn
Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	June 22, 2011; 1:00PM EST
MEETING ENDING DATE AND TIME	June 22, 2011; 2:00PM EST
PURPOSE OF MEETING	Industry meeting
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	White Oak Bldg #22, Rm #1419
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	No
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	Jagjit Grewal Senior Regulatory Health Project Manager WO Bldg #22, Rm #5109 301-796-0846
ESCORT INFORMATION (If different from Hosting Official)	Same

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/s/

JAGJIT S GREWAL
05/16/2011



NDA 022175

INFORMATION REQUEST

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) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pertzye (pancrelipase) Delayed-Release Capsules.

We are reviewing the Drug Master File (DMF) in support of your NDA and have the following comments. We request a prompt written response in order to continue our evaluation of your NDA.

(b) (4) DMF (b) (4) has been found to contain deficiencies. A letter has been sent to (b) (4) listing the deficiencies. (b) (4) should address the deficiencies by submitting the information directly to the DMF. Please notify us when (b) (4) has submitted the requested information.

If you have any questions, or would like to request a meeting, call Matthew Scherer, Regulatory Project Manager, at (301) 796-2307.

Sincerely,

{See appended electronic signature page}

Brian K. Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

BRIAN K STRONGIN
10/27/2010



NDA 022175

INFORMATION REQUEST

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) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pertzye (pancrelipase) Delayed-Release Capsules.

We also refer to your February 17, 2010, March 24, 2010, and July 29, 2010, submissions that constitute a complete response to our August 27, 2009, action letter.

We are reviewing the clinical section of your submissions and have the following information request. We request a prompt written response in order to continue our evaluation of your NDA.

Provide 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.

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at (301)796-2307.

Sincerely,

{See appended electronic signature page}

R. Wesley Ishihara
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

RICHARD W ISHIHARA
09/23/2010



NDA 022175

ACKNOWLEDGE CLASS 2 RESPONSE

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

Dear Dr. Sipos:

We acknowledge receipt on July 29, 2010 of your July 29, 2010 resubmission to your new drug application for Pertzye (pancrelipase) Delayed-Release Capsules.

We also acknowledge receipt of your February 17, 2010 and March 24, 2010 submissions.

We consider these submissions to be a complete, class 2 response to our August 27, 2009 action letter. Therefore, the user fee goal date is January 29, 2011.

If you have any questions, call me at (301) 796-2307.

Sincerely,

{See appended electronic signature page}

Matthew Scherer, M.B.A.
Senior Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22175

ORIG-1

DIGESTIVE CARE
INC

PANCRECARB

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/s/

MATTHEW C SCHERER

08/21/2010



NDA 022175

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Digestive Care, Inc.
1120 Win Drive
Bethlehem, PA 18017-7059

ATTENTION: Tibor Sipos, Ph.D
President

Dear Dr. Sipos:

Please refer to your New Drug Application NDA dated October 27, 2008, received October 27, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pancrelipase Capsules, 4000, 8000, and 16,000 USP units of lipase.

We also refer to your March 25, 2010, correspondence, received March 25, 2010, requesting review of your proposed proprietary name, Pertzye. We have completed our review of the proposed proprietary name, Pertzye and have concluded that it is acceptable.

The proposed proprietary name, Pertzye, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your March 25, 2010 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nitin M.Patel, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5412. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Elizabeth Ford at (301) 796-5412.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22175

ORIG-1

DIGESTIVE CARE
INC

PANCRECARB

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/s/

CAROL A HOLQUIST

06/11/2010



NDA 022175

ACKNOWLEDGE INCOMPLETE RESPONSE

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

Dear Dr. Sipos:

We acknowledge receipt on March 24, 2010 of your March 24, 2010 submission to your new drug application (NDA) for Pancrecarb (pancrelipase) Delayed-Release Capsules.

We do not consider this a complete response to our action letter. Therefore, the review clock will not start until we receive a complete response. The following deficiencies from our action letter still need to be addressed:

1. 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.
2. You have not included analytical techniques that monitor product degradation such as, but not limited to, HPLC.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a partial waiver and partial deferral of pediatric studies for this application. Once the review of this application is complete, we will notify you whether we have waived/deferred the pediatric study requirement for this application.

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

Sincerely,

{See appended electronic signature page}

Elizabeth A.S. Ford, R.N.
Senior Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22175

ORIG-1

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/s/

ELIZABETH A FORD

04/13/2010



NDA 022175

ACKNOWLEDGE INCOMPLETE RESPONSE

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

Dear Dr. Sipos:

We acknowledge receipt on February 18, 2010 of your February 17, 2010 submission to your new drug application (NDA) for Pancrecarb (pancrelipase) Delayed-Release Capsules.

We do not consider this a complete response to our action letter. Therefore, the review clock will not start until we receive a complete response. The following deficiencies from our action letter still need to be addressed:

You provided a summary response to each issue identified by the Agency in the August 27, 2009 complete response letter, with hyperlinks to supporting documents and data. However, many of the Product Quality hyperlinks (dci-response-fdacrlt.pdf) are not functioning, and we do not have access to your supporting documents and data. In addition, the Clinical Pharmacology response hyperlinks in your response document (dci-response-fdacrlt.pdf) are not functioning. Therefore, we are unable to perform a meaningful review of your submission. Resubmit your response with functioning hyperlinks, and provide the exact location of the Clinical Pharmacology hyperlinked files (i.e., protease TMV-043, lipase TMV-047, TMV-047, Report RR-166). We need the exact path of the file with folder names to locate those files.

We have the following additional Biopharmaceutics Comments:

1. Your proposed dissolution methodology (No. TM-6007) is not optimal, and it is different from the USP dissolution method for pancrelipase capsule products as shown below.
 - Your dissolution testing in the acid stage lasted for 30 minutes; the USP method calls for a period of 60 minutes.
 - Your dissolution testing in the buffer stage used fortified intestinal fluid (pH 6.0) with the addition of olive oil substrate, casein substrate, and starch substrate; the USP method employed a phosphate buffer (pH 6.0).
2. It is not known if the lower % label claim on initial dissolution testing at month zero, i.e., (b) (4) (at 30 minutes in the buffer stage), [Table (3.2.P.8.1.)2 Module 3.2.P.8.1, p. 4] was due to the different dissolution media that were employed. In the table identified above, you reported the initial mean % label claim of (b) (4) at month zero of the same lots for stability testing.

The above concerns on differences in % label claim were raised in the Agency's preliminary responses to your questions which were to be discussed in the November 3, 2009 meeting. However, the meeting was cancelled after you received the Agency's responses.

3. Consider adopting the USP method or provide justification for the differences with the method you are proposing.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a partial waiver and partial deferral of pediatric studies for this application. Once the review of this application is complete, we will notify you whether we have waived/deferred the pediatric study requirement for this application.

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

Sincerely,

{See appended electronic signature page}

Brian K. Strongin, R.Ph, M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22175

ORIG-1

DIGESTIVE CARE
INC

PANCRECARB

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/s/

BRIAN K STRONGIN

03/16/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022175

Preliminary Comments

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) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pancrecarb (pancrelipase) Capsules.

We also refer to the scheduled meeting between representatives of your firm and the FDA on November 3, 2009. The purpose of the meeting is to discuss issues related to the deficiencies identified in the Complete Response Letter dated August 27, 2009.

A copy of our preliminary responses to your questions, and any additional comments in preparation for the discussion at the meeting, is attached for your information. This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact the Regulatory Project Manager). If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face-to-face to teleconference). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions.

Please note that if there are any major changes to your development plan, the purpose of the meeting or to the questions, based on our responses herein, we may not be prepared to discuss or reach agreement on such changes at the meeting. If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Project Manager to discuss the possibility of including these for discussion at the meeting.

If you have any questions, call me at (301) 796-0193.

Sincerely yours,

{See appended electronic signature page}

Elizabeth A.S. Ford, R.N.
Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Question 1: Does the Agency agree that the type of information provided will be sufficient

(b) (4)

If the Agency disagrees, what additional information would the Agency require to support this change?

FDA Response to Question 1:

Yes, provided that all CMC issues that we identified in regard to the manufacturing of the MS-16 capsules and conveyed to you in our letter of August 27, 2009 have been satisfactorily addressed. Additionally, process validation reports for the manufacturing of the To-be-Marketed-Product (TbMP) (b) (4) MS-8, and MS-16 capsules should also be provided.

Question 2: Does the Agency agree that this approach to establishing a shelf-life for the drug product made using (b) (4) is acceptable?

FDA Response to Question 2:

No. To establish the product shelf life, real time, real temperature stability data should be collected on the To-be-Marketed-Product (TbMP) (b) (4) MS-8 and MS-16 dosage strengths packaged in the commercial container closure system and results of the studies provided. Refer to ICH Guidelines Q1A (R2) for guidance on stability studies for drug product. Specifications for capsule weight, product purity/impurities assessed by RP-HPLC should also be included in your stability study.

Question 3: Does the Agency agree that the same type of information submitted for (b) (4) as summarized in Question 1, would be acceptable to support approval of an additional dosage strength?

If the Agency disagrees, what additional information would the Agency require to support an additional dosage strength?

FDA Response to Question 3:

Please refer to the answers to Question 1 and Question 2.

Question 4: When will the Agency provide confirmation that DCI's and (b) (4) proposed corrective action plans are sufficient to achieve satisfactory resolution of the deficiencies to enable approval of NDA 22-175?

Will follow-up facility inspections at both DCI and (b) (4) be required to verify the corrections prior to approval of NDA 22-175?

FDA Response to Question 4:

4a. The proposed corrective actions are currently under review by CDER DMPQ and ORA district offices. Further information will be requested as necessary.

4b. Follow-up inspections at DCI and (b) (4) may be required to verify corrections to the application and compliance with current good manufacturing practices. These inspections are not required to be pre-announced and it is not CDER policy to communicate this information. If it is determined that a reinspection is necessary, the Agency may provide prior notice, but not typically more than a week in advance.

Question 5: Does the Agency agree that the proposed physicochemical characterization and validation plan will be sufficient to support a submission to qualify (b) (4) as an alternative API supplier under the PANCRECARB® NDA 22-175?

5b If the Agency disagrees with this approach, what additional information would the Agency require to support qualification of the (b) (4) API for use in the PANCRECARB® drug product?

5c If the PANCRECARB® drug product made with the (b) (4) API is comparable with the drug product made with the (b) (4) API, would the Agency agree that a (b) (4) shelf-life could be assigned to the drug product made using the (b) (4) API prior to completion of real time stability studies?

5d If the data do not support a conclusion that the PANCRECARB® drug product made with the (b) (4) API is comparable with the drug product made with the (b) (4) API, what information would the Agency require to support qualification of the (b) (4) API for use in the PANCRECARB® drug product under NDA 22-175?

FDA Response to Question 5:

No. We understand that you plan to use drug substances from both (b) (4) and (b) (4) to manufacture Pancrecarb. This proposal is not acceptable. Drug product manufactured using (b) (4) drug substance will be considered different from drug product manufactured using (b) (4) drug substance. As stated in the FDA Guidance for Industry: Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs: “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.”

If you choose to use the (b) (4) drug substance, a possible path forward would be to exclusively use (b) (4) drug substance to manufacture Pancrecarb under this NDA. In this case, one or more clinical trials which demonstrate the efficacy of your To-be-

Marketed-Product (TbMP) derived from (b)(4) drug substance (DS) will be required to gain approval. In addition, you will be required to provide manufacturing information, process validation, and release and stability testing protocols and data for the (b)(4) DS-derived TbMP to support your application.

Question 6: 6a. Would the Agency consider (b)(4) variability in capsule fill weight to be acceptable?

6b. Would the Agency consider titration of the lipase potency with (b)(4) as an acceptable alternative approach to reduce the capsule fill weight variability?

FDA Response to Question 6:

6a. No. Capsule fill weight variability should be well controlled in your manufacturing process, and reflect your manufacturing process history and capability.

6b. You have not provided sufficient information in your meeting package for us to answer this question.

Question 7: 7a Does the Agency agree that the microspheres packaged as described would satisfy the requirements for an age appropriate formulation/dosage form?

7b If the Agency disagrees, what would the Agency require to satisfy the requirement for an age appropriate formulation/dosage form?

FDA Response to Question 7:

No. Real time, real temperature stability data on the product packaged in the container closure system intended for commercial use should be provided. Additionally, studies addressing product dissolution and disintegration profiles, and the effects of pH (pH 3-6) and temperature (37°C-45°C) on drug product dissolved in various brands of infant formulas and breast milk should be conducted.

Additional Biopharm Comments:

As stated in the Complete Response letter, your proposed dissolution specification for lipase ($Q = (b)(4)$ at 30 min) is not acceptable. You reported that at the initial release at Month "0", the potency is close to (b)(4) but the dissolution showed only (b)(4) for the MS 16 lot No. 6K09B (also the biolot; Ps. 9-10/17 under Module 3.2.P.8 Stability Summary).

You further stated in the study report No. RR-075 for *in vitro* stability of Pancrecarb when exposed to applesauce that the initial potency is (b)(4) at "0" minute and above (b)(4) of total lipase activity was retained for MS 4, MS 8, and MS 16 microspheres after 40 to 60 minutes.

Please provide further details and rationale/justifications for the differences in the results and please state whether different assays were used contributing to the differences in results. If different assay methodologies were used, a conversion factor between the assay methodologies should be used to correct the different IU obtained.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22175	GI-1	DIGESTIVE CARE INC	PANCRECARB

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/s/

ELIZABETH A FORD
11/02/2009

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Meeting Cancellation Form

(Use this form to cancel a meeting that was granted and scheduled after which time the sponsor or FDA has subsequently cancelled.)

Please remember to update the Meeting Status field in IMTS for this cancellation.

Complete the information below and check form into DFS.

Application Type	<input type="checkbox"/> P-IND <input type="checkbox"/> IND <input checked="" type="checkbox"/> NDA
Application Number	NDA 022175
DATE Meeting Cancelled (per communication with requester)	November 3, 2009
Scheduled Meeting Date	November 3, 2009
Reason for Cancellation	Sponsor requested meeting cancellation following receipt of preliminary responses, and clarification of preliminary response #2.
Project Manager	Elizabeth A.S. Ford, R.N.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22175	GI-1	DIGESTIVE CARE INC	PANCRECARB

Meeting ID	Regulatory Program	Meeting Type	Meeting Code	Meeting Status
27722	None	A	Other	Canceled

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/s/

ELIZABETH A FORD
11/03/2009

From: (b) (4)
Sent: Tuesday, November 03, 2009 10:15 AM
To: Ford, Elizabeth
Subject: RE: Preliminary Comments

Dear Ms. Ford:

DCI plans to continue to use (b) (4) as the sole drug substance to manufacture Pancrecarb. At some time in the future, DCI would plan to further engage the Division in a discussion about the specific requirements to obtain approval of the drug product manufactured using the (b) (4) drug substance.

We appreciate the Division's responses to our questions, and are hereby confirming that our teleconference scheduled for this afternoon can be canceled.

Thank you,
(b) (4)

From: Ford, Elizabeth [mailto:Elizabeth.Ford@fda.hhs.gov]
Sent: Tuesday, November 03, 2009 9:51 AM
To: (b) (4)
Cc: Ford, Elizabeth
Subject: RE: Preliminary Comments
Importance: High

Dear Ms. (b) (4)

Please clarify which drug substance (b) (4) you plan to use to manufacture Pancrecarb.

In regards to Digestive Care's request that we confirm that SDS-PAGE is acceptable and sufficient to monitor product purity/ impurity for release and stability:

SDS-PAGE alone is not adequate to monitor product purity/impurity for release and stability. Digestive Care was advised to include additional assays, such as RP-HPLC, in their release and stability programs in the CR letter issued on August 27, 2009.

Please confirm the status of the teleconference scheduled for this afternoon. A call-in number has not been provided.

Thanks,
Elizabeth Ford

Elizabeth A.S. Ford, RN
Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation Research III
CDER/FDA
(301) 796-0193

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If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-1218. Thank you.

From: (b) (4)
Sent: Monday, November 02, 2009 4:47 PM
To: Ford, Elizabeth
Subject: RE: Preliminary Comments

Hi Elizabeth:

Thank you for providing the Agency's preliminary comments. We are requesting clarification on Question 2 as indicated in the attached.

Given clarification of this item, we are prepared to cancel the teleconference currently scheduled for tomorrow Nov. 3rd at 4pm.

Thank you in advance for a reply.

Best Regards,

(b) (4)

(b) (4)

From: (b) (4)
Sent: Monday, November 02, 2009 12:08 PM
To: 'Ford, Elizabeth'
Subject: RE: Preliminary Comments

Hi:

All pages received.

Thank you,

(b) (4)

From: (b) (4)
Sent: Monday, November 02, 2009 11:49 AM
To: 'Ford, Elizabeth'
Subject: RE: Preliminary Comments

Hi Elizabeth:

Please fax to (b) (4)

Thank you,

(b) (4)

From: Ford, Elizabeth [mailto:Elizabeth.Ford@fda.hhs.gov]
Sent: Monday, November 02, 2009 10:22 AM
To: (b) (4)
Subject: Preliminary Comments
Importance: High

Hello,

Please provide either a fax number, or an email account (secure), to send the preliminary comments to.

Thanks,
Elizabeth

Elizabeth A.S. Ford, RN
Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation Research III
CDER/FDA
(301) 796-0193

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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PDF attachment, from [REDACTED]^{(b) (4)} to Elizabeth Ford, received in combination with electronic mail dated 11/2/2009. PDF document entitled “DCI question.pdf”

Please provide clarification to Question 2, as follows:

Based on previous guidance from the Agency, DCI has routinely implemented and believes that Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) is sufficient to control the quality of the product for release and stability.

In the CR Letter dated August 27, 2009, the Agency stated the following:

- I. **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.**

In a submission dated August 11, 2009, DCI provided the following information in response to this same item which also appeared in the Division's letter dated July 10, 2009.

SDS-PAGE is frequently used to characterize and analyze complex protein mixtures because of its ability to clearly resolve the individual proteins into distinct bands. The banding pattern (number of bands, relative migrations and relative amounts of each band) is characteristic for a given mixture of proteins and additional bands would represent impurities. DCI currently employs SDS-PAGE to monitor for product-related and process related impurities in the PANCRECARB[®] drug product for release and stability.

In the Agency's response dated November 2, 2009, for the Type A Meeting Question 2, it states the following:

FDA Response to Question 2:

No. To establish the product shelf life, real time, real temperature stability data should be collected on the To-be-Marketed-Product (TbMP) (b) (4) MS-8 and MS-16 dosage strengths packaged in the commercial container closure system and results of the studies provided. Refer to ICH Guidelines Q1A (R2) for guidance on stability studies for drug product. Specifications for capsule weight, product purity/impurities assessed by RP-HPLC should also be included in your stability study.

Please confirm that SDS-PAGE is acceptable and sufficient to monitor product purity/impurity for release and stability.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22175

GI-1

DIGESTIVE CARE
INC

PANCRECARB

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/s/

ELIZABETH A FORD
11/03/2009



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022175

MEETING GRANTED

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) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pancrecarb.

We also refer to your September 18, 2009 correspondence, requesting a meeting to discuss issues related to the deficiencies identified in the Complete Response Letter dated August 27, 2009. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting.

The meeting is scheduled as follows:

Date: November 3, 2009
Time: 4:00 PM – 5:00 PM
Phone Arrangements: FDA will call Digestive Care, Inc. at a number to be provided by Digestive Care, Inc.

CDER Participants:

NAME	OFFICE/DIVISION	TITLE
Julie Beitz, M.D.	Office of Drug Evaluation III	Director
Donna Griebel, M.D.	Division of Gastroenterology Products	Director
Ruyi He, M.D.	Division of Gastroenterology Products	Acting Deputy Director
Anil Rajpal, M.D.	Division of Gastroenterology Products	Medical Team Leader
Marjorie Dannis, M.D.	Division of Gastroenterology Products	Medical Officer
Jang-Ik Lee, Ph.D.	Division of Clinical Pharmacology and Biopharmaceutics III	Clinical Pharmacology and Biopharmaceutics
Jane Bai, Ph.D.	Division of Clinical Pharmacology	Clinical Pharmacology and

	and Biopharmaceutics II	Biopharmaceutics Reviewer
Tamal Chakraborti, Ph.D.	Division of Gastroenterology Products	Pharmacology Reviewer
Sushanta Chakder, Ph.D.	Division of Gastroenterology Products	Pharmacology Team Leader
Howard Anderson, Ph.D.	Division of Therapeutic Proteins	Chemistry Reviewer
Wei Guo, Ph.D.	Division of Therapeutic Proteins	Chemistry Reviewer
Emanuela Lacana, Ph.D.	Division of Therapeutic Proteins	Acting Associate Lab Chief
Barry Cherney, Ph.D.	Division of Therapeutic Proteins	Deputy Director
Gibbes Johnson, Ph.D.	Division of Therapeutic Proteins	Chief, Lab of Chemistry
Patrick Marroum, Ph.D.	Office of New Drug Quality Assessment	Special Assistant to the Office Director
Tien Mien Chen, Ph.D.	Office of New Drug Quality Assessment	Biopharmaceutics Reviewer
Elizabeth Ford, R.N.	Division of Gastroenterology Products	Project Manager

Provide the background information for the meeting (three copies to the application and 19 desk copies to me) at least two weeks prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by October 7, 2009, we may cancel or reschedule the meeting.

If you have any questions, call me at (301) 796-0193.

Sincerely,

[See appended electronic signature page]

Elizabeth A. S. Ford, R.N.
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application
Type/Number

Submission
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Submitter Name

Product Name

NDA-22175

GI-1

DIGESTIVE CARE
INC

PANCRECARB

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/s/

ELIZABETH A FORD
10/01/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 022175

**RECONSIDERATION REQUEST
ADVICE/ACKNOWLEDMENT**

Digestive Care, Inc.
1120 Win Drive
Bethlehem, Pennsylvania 18017

ATTENTION: Tibor Sipos, Ph.D.
President

Dear Dr. Sipos:

Please refer to your New Drug Application (NDA) dated October 27, 2008, received October 27, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pancrelipase Capsules, (b) (4) 8000, and 16,000 USP units of lipase.

We also refer to your June 29, 2009, correspondence, received June 29, 2009, requesting reconsideration of your proposed proprietary name, Pancrecarb.

We have reviewed your request for reconsideration of the name Pancrecarb and have the following comments:



Therefore, we defer our decision on the proprietary name Pancrecarb, until after you have responded to the Agency's Complete Response letter.

We recommend that a 'Request for Proprietary Name Review' be submitted for this product once all the product characteristics of the to-be-marketed Pancrecarb formulation are firmly established.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nina Ton, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-1648. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Elizabeth Ford at 301-796-0193.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh

Director

Division of Medication Error Prevention and Analysis

Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22175	ORIG-1	DIGESTIVE CARE INC	PANCRECARB

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/s/

MELINA N GRIFFIS
09/25/2009

CAROL A HOLQUIST
09/25/2009

MEMORANDUM OF TELECON

DATE: June 24, 2009

APPLICATION NUMBER: NDA 22-175

BETWEEN:

Name: Tibor Sipos, Ph.D., President of DCI
Bill Humphries; VP of Marketing for DCI
[REDACTED] (b) (4)

Phone: [REDACTED] (b) (4)

Representing: Digestive Care, Incorporated

AND

Name: Julie Beitz, M.D., ODE III Director
Donna Griebel, M.D., Director
Anne Pariser, M.D., Acting Deputy Director
Anil Rajpal, M.D., Acting Team Leader
Marjorie Dannis, M.D., Medical Officer
Sushanta Chakder, Ph.D., Supervisory Pharm/Tox Reviewer
Tamal Chakraborti, Ph.D., Pharm/Tox Reviewer
Freda Cooner, Ph.D., Statistical Reviewer
Wei Guo, Ph.D., Chemistry Reviewer
Elizabeth Ford, R.N., Regulatory Health Project Manager
Division of Gastroenterology Products

SUBJECT: NDA 22-175, Pancrecarb, June 15, 2009 FDA Information Request

The FDA issued a clinical information request on February 27, 2009 requesting the submission of a partial pediatric waiver request (for patients aged less than 1 month), a pediatric deferral request (for studies in patients aged 1 month to less than 2 years), and a pediatric plan for NDA 22-175. In an IR letter issued June 15, 2009, the FDA amended that request, no longer requiring the submission of a pediatric deferral. In a follow-up email communication, [REDACTED] (b) (4) indicated that Digestive Care no longer intends to perform additional pediatric studies and requested clarification of the need to submit a pediatric plan. The FDA agreed that the pediatric plan would not be required given that the company no longer intends to perform additional pediatric studies.

The second component of the June 15, 2009 IR letter indicated that each of the [REDACTED] (b) (4) Pancrecarb formulations differ from one another such that comparability of the [REDACTED] (b) (4) formulations relative to one another has not been shown by the information provided in the NDA submission. The letter further indicated that additional clinical studies may be required to approve the [REDACTED] (b) (4) MS-8

strengths. The FDA and Digestive Care agreed that [REDACTED] (b) (4) [REDACTED] without the need for additional clinical studies, provided the additional CMC testing would be performed and submitted to the NDA for review.

[REDACTED] (b) (4)

The applicant was informed that [REDACTED] (b) (4) they will need to do another rigorous clinical study, similar to the pivotal study for MS-16, to show efficacy [REDACTED] (b) (4). The Sponsor expressed concern that it would be unethical to enroll young patients (those typically requiring G-tubes) in a placebo controlled trial; we told them it would be acceptable to use older patients for the study and extrapolate the data obtained for younger patients.

[REDACTED] (b) (4)

[REDACTED] This proposal should be submitted to the IND for FDA review. Digestive Care agreed to submit their proposal to their IND.

The call was concluded at 11:00 AM.

Elizabeth A.S. Ford, R.N.
Regulatory Health Project Manager

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22175	----- ORIG 1	----- DIGESTIVE CARE INC	----- PANCRECARB

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/s/

ELIZABETH A FORD
07/31/2009
6/24 t-con minutes

MEMORANDUM OF TELECON

DATE: July 13, 2009

APPLICATION NUMBER: NDA 22-175

BETWEEN:

Name: Tibor Sipos, Ph.D., President of DCI
Bill Humphries; VP of Marketing for DCI
 (b) (4)
Jules Mitchel; Regulatory Consultant
Glen Park; Regulatory Consultant

Phone:  (b) (4)

Representing: Digestive Care, Inc.

AND

Name: Julie Beitz, M.D., ODE III Director
Donna Griebel, M.D., Director
Anne Pariser, M.D., Acting Deputy Director
Anil Rajpal, M.D., Acting Team Leader
Sushanta Chakder, Ph.D., Supervisory Pharm/Tox Reviewer
Tamal Chakraborti, Ph.D., Pharm/Tox Reviewer
Wei Guo, Ph.D., Chemistry Reviewer
Emanuela Lacana, Ph.D., Acting Associate Lab Chief
Jane Bai, Ph.D. Clinical Pharmacology Reviewer
Elizabeth Ford, R.N., Regulatory Health Project Manager
Division of Gastroenterology Products

SUBJECT: Target Date/Communication of Labeling PMRs/PMCs

The timeline for communication of labeling comments and PMR/PMC requests was included in the filing communication letter for NDA 22-175; the target date was identified as July 13, 2009. Significant deficiencies have been identified with the application, which now preclude discussion of labeling by the target date. A teleconference was therefore scheduled with Digestive Care Inc. A chemistry manufacturing and controls (CMC) discipline review letter was issued on July 10, 2009, and a copy of this letter was faxed to the applicant in advance of the teleconference.

Digestive Care was informed that deficiencies in the application preclude discussion of labeling; however, the following PMRs were communicated to the applicant:

1. Requirement for development of an age appropriate formulation for Pancrecarb (pancrelipase) Delayed-Release Capsules: Develop an age appropriate formulation to allow for dosing to the youngest, lowest weight pediatric patients, including infants less than 12 months of age who will be administered 2,000 to 4,000 lipase units per 120 mL of formula or per breast-feeding.

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

Digestive Care acknowledged understanding of the above-mentioned PMRs, and acknowledged receipt of the CMC discipline review letter. In addition, they indicated that a CMC amendment, containing information needed for the (b) (4) MS-8 strengths, was being prepared for submission to the NDA shortly.

The Division indicated that the sponsor could submit the information requested, but that given the current point in the review cycle, any additional amendments to the application may not be reviewed in the current review cycle. The Division reminded the applicant that the REMS/Medguide was also an outstanding requirement to the application, and inquired about the status of this submission.

Digestive care indicated they are continuing to work on the REMS/Medguide; however, due to the ongoing support required as part of their pre-approval inspection, they are still 2 to 3 weeks away from being able to submit the requested information.

Regarding the CMC DR letter issued on July 10, 2009, Digestive Care requested clarification on the following issues:

- **Item #7:** Provide a description of your qualification program for incoming 1206 and 1208 drug substances.

The Division requested the location of the SOP within the application. At the time of the call, the applicant was unsure if the SOP was included, and asked if the presence of an acceptable SOP would resolve the matter. The Agency requested the applicant submit the SOP for review and evaluation.

- **Item # 11:** Provide detailed information regarding the chemistry, manufacturing and controls for the Cellulose acetate phthalate and Diethyl phthalate used for (b) (4) of the product.

The applicant asked if it would be sufficient to provide the DMF number to resolve this deficiency. The Agency indicated that if an active DMF was identified, this should provide the necessary information.

The Division reminded the applicant that there are a large number of deficiencies to be addressed. If the applicant plans to submit a response to all of the outstanding deficiencies before the end of the review cycle, the Division would evaluate the significance of each submission when it is received, and make a determination whether to review the submission during the current review cycle, or review it during the next review cycle.

Elizabeth A.S. Ford, R.N.
Regulatory Health Project Manager

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/s/

ELIZABETH A FORD

07/31/2009

Target Date communications



NDA 22-175

DISCIPLINE REVIEW LETTER

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

Dear Dr. Sipos:

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

Our review of the Chemistry, Manufacturing and Controls section of your submission is complete, and we have identified the following deficiencies:

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 address the purity/impurities profile 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.
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) contents as a combination of all solvents measured. Provide acceptance criteria for each of the (b) (4) separately.
 - e. Expiry dating for 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 in using (b) (4), in addition to gelatin capsule, 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 reprocessing steps in your manufacturing process. Provide studies you have conducted and documentation of procedures you have in place to support reprocessing.
 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 (b) (4) drug substance used to manufacture (b) (4) MS8 and the homogeneity of the (b) (4) drug substance used to manufacture MS16.
 5. Due to the critical role of (b) (4) in lipase activity, adequate control of (b) (4) activity must be ensured in drug product. Provide information that demonstrates you have control of (b) (4).
 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 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 regards to your analytical methodologies, we have the following comments:

- a. The assessment of linearity for the lipase and protease assays is conducted using (b) data points. We recommend a minimum of 5 data points for determination of assay linearity.
 - b. Clarify your acceptance criterion for lipase assay linearity.
 - c. To support validation of (b) (4) assay precision, clarify the amounts of (b) (4) used during assay validation.
11. Provide detailed information regarding the chemistry, manufacturing and controls for the Cellulose acetate phthalate and Diethyl phthalate used for (b) (4) 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.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

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

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Brian Strongin
7/10/2009 03:15:57 PM



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-175

MEETING DENIED

Digestive Care, Inc.
1120 Win Drive
Bethlehem, PA 18017

Attention: Tibor Sipos, Ph.D.
President

Dear Dr. Sipos:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pancrecarb Capsules, (b)(4), 8000, and 16,000 USP units of lipase.

We also refer to your June 11, 2009, correspondence requesting a teleconference to discuss our finding that the proposed proprietary name Pancrecarb was unacceptable. We are denying the meeting request because we feel that it is unnecessary. Per our June 24, 2009 telephone conversation please submit the data and arguments contained in your June 11, 2009 submission as a formal request for reconsideration of the proposed proprietary name Pancrecarb. Once we have had a chance to review the reconsideration request, we will provide you with our decision and a teleconference can be held at that time if further discussion is needed.

If you have any questions, call Nina Ton, Safety Regulatory Project Manager at (301) 796-1648.

Sincerely,

{See appended electronic signature page}

Carol Holquist, R.Ph.
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

Carol Holquist
6/30/2009 02:09:20 PM



NDA 22-175

INFORMATION REQUEST LETTER

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

Dear Dr. Sipos:

Please refer to your October 27, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pancrecarb (pancrelipase) Capsules.

We also refer to your submissions dated December 5, 2008, December 8, 2008, December 11, 2008, December 15, 2008, March 13, 2009, March 17, 2009, and June 3, 2009.

We additionally refer to the Information Request (IR) letter we sent to you, dated February 27, 2009, in which we requested that you submit a partial pediatric waiver request (for patients aged less than 1 month), a pediatric deferral request (for studies in patients aged 1 month to less than 2 years), and a pediatric plan for NDA 22-175.

We are reviewing your submission, and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your application.

1. Regarding the pediatric partial waiver, deferral, and plan requests, we have the following clarifications:

- a. We no longer require that you submit a pediatric deferral request to include patients aged 1 month to less than 2 years. (b) (4)



- b. We continue to request that you submit a partial waiver request for pediatric patients aged birth to less than 1 month, and a pediatric plan that would include a

general description of the pediatric studies to be conducted and a timeline for these studies.

- c. For the pediatric studies that you have already conducted, should your product be approved, you will be able to include the safety and efficacy results from these pediatric studies in the labeling, which may appear in the Use in Specific Populations, Pediatric Use (Section 8.4), Clinical Studies (Section 14), and Adverse Reactions (Section 6) sections of the labeling.
2. We note that each of the Pancrecarb formulations ((b) (4) MS-8, and MS-16) differ from one another. (b) (4)
- (b) (4) Thus, comparability of the (b) (4) formulations relative to one another has not been shown by the Chemistry, Manufacturing, and Controls (CMC) information provided in your submission. Since your pivotal trial (Study 06-001) was conducted using only the MS-16 formulation, and because the studies submitted for (b) (4) MS-8 are not adequate to demonstrate the effectiveness of the (b) (4) MS-8 formulations, we are unable to determine the efficacy of the (b) (4) MS-8 formulations. One or more additional clinical trials will be required to demonstrate the efficacy of the (b) (4) MS-8 formulations in order to gain approval of (b) (4) formulations.

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

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Brian Strongin
6/15/2009 09:04:08 AM



NDA 22-175

DISCIPLINE REVIEW LETTER

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) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pancrecarb (pancrelipase) Delayed-Release Capsules.

Our review of the Microbiology section of your submission is complete, and we have the following comments:

USP Chapter <1111> and the methods provided in Chapters <61> and <62> have been revised as of May 1, 2009. The acceptable limits for nonaqueous preparations for oral use are as follows:

- Total Aerobic Microbial count = 103 CFU/g or mL which translates to a maximum acceptable count of 2000 CFUs.
- Total acceptable combined yeast/molds count = 102 CFU/g or mL or 200 CFUs.
- Absence of *Escherichia coli*.

We recommend that you update your microbial limits requirement to the revised USP specifications.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

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

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Brian Strongin
5/28/2009 10:41:51 AM



NDA 22-175

INFORMATION REQUEST LETTER

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

Dear Dr. Sipos:

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

We are reviewing the Dissolution and Biopharmaceutical sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. The submitted data do not support the proposed dissolution limit of (b) (4) (Q) in 30 minutes. However, based on the provided information a limit of (b) (4) (Q) in 30 minutes would be acceptable
2. The proposed 24 month expiration dating period, when stored at controlled room temperature, is not justified. Based on the acceptable dissolution limit of (b) (4) (Q), an expiration dating period of (b) (4) 12 months for formulations MS-8 and MS-16, could be granted.
3. The experimental procedures described in Protocol RR-075, and in amendment 1.2 for testing the stability of your product when mixed with applesauce, are considered inappropriate. We request you repeat the applesauce stability study according to the procedure described below:

(b) (4)

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

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Brian Strongin
5/7/2009 04:16:27 PM



NDA 22-175

INFORMATION REQUEST LETTER

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

Dear Dr. Sipos:

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

We are reviewing the Statistical and Biopharmaceutical sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. In your Clinical Study Report for Study 06-001 you stated that “[s]ubjects who... were randomized but withdrew prior to completion of Treatment Period 2 were replaced with a new subject.” Identify the replacing subjects and the subjects who were replaced. You should also provide the details of the replacement procedure and discuss any impact on the randomization scheme.
2. Regarding the database audit findings discussed on page 42 of your Clinical Study Report for Study 06-001, provide additional details on the audit findings and data queries along with the original datasets. We recommend you provide a comprehensive table identifying all the revisions to the datasets.
3. For the bioavailability study 092206, you did not correct for the baseline levels when calculating the % lipase activities recovered in the duodenum. Re-calculate the % activities with corrections for baseline levels.
4. For the bioavailability study 092206, you used duodenal fluid in your analytical validation, but did not include gastric fluid. An analytical validation report with gastric fluid is needed as well.
5. For the bioavailability study 092206, you did not use human lipase and other human enzymes as the markers on the SDS-PAGE gel. Identify the specificities of your SDS-PAGE results for individual enzymes, and clarify whether or not human

enzymes overlap with porcine enzymes on SDS-PAGE gel. In addition, provide the Molecular weights of individual human enzymes and show where human enzyme bands will be if run together with gastric or duodenal aspirates.

6. Please define the components and composition of the Lundh test meal used in the bioavailability study.
7. For the bioavailability study 092206, please provide the AUC (% of total activity recovered in gastric or duodenal aspirate) for each enzyme in Phase 1 after placebo.

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

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Richard W Ishihara
4/9/2009 10:48:22 AM
Signing for Brian Strongin



NDA 22-175

**PROPRIETARY NAME REQUEST
- UNACCEPTABLE**

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

Dear Dr. Sipos

Please refer to your New Drug Application (NDA) dated October 27, 2008, received October 27, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pancrelipase Capsules, (b) (4) 8000, and 16,000 USP units of lipase.

We also refer to your December 4, 2008 correspondence, received December 5, 2008 requesting review of your proposed proprietary name, Pancrecarb. (b) (4)

We have completed our review of this proposed proprietary name(s) and have concluded that this name(s) is unacceptable for the following reasons.

(b) (4)

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the draft Guidance for Industry, *Complete Submission for the Evaluation of Proprietary Names*, [HTTP://www.fda.gov/cder/guidance/7935dft.pdf](http://www.fda.gov/cder/guidance/7935dft.pdf) and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Nina Ton, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-1648. For any other information regarding this application contact Elizabeth Ford, Regulatory Health Project Manger in the Office of New Drugs (OND) .

Sincerely,

{See appended electronic signature page}

Anne Pariser, M.D.
Acting Deputy Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Anne Pariser

4/8/2009 03:43:01 PM



NDA 22-175

INFORMATION REQUEST LETTER

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

Dear Dr. Sipos:

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

We are reviewing your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your application.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if the FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). This provision took effect on March 25, 2008.

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.

Your proposed REMS must include the following:

Medication Guide: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Pancrecarb (pancrelipase) Delayed-Release Capsules poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Pancrecarb (pancrelipase) Delayed-Release Capsules. FDA has determined that Pancrecarb (pancrelipase) Delayed-Release Capsules is a product that is important to health and patient adherence to directions for use is crucial to the drug's effectiveness. FDA has also determined that Pancrecarb (pancrelipase) Delayed-Release Capsules is a

product for which patient labeling could help prevent serious adverse events. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Pancrecarb (pancrelipase) Delayed-Release Capsules.

Timetable for Submission of Assessments: The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than by 18 months, 3 years, and in the 7th year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

In accordance with section 505-1, before we can continue our evaluation of NDA 22-175, you will need to submit the proposed REMS to this application. The REMS, once approved, will create enforceable obligations.

We suggest that your proposed REMS submission include two parts: a “Proposed REMS” and a “REMS Supporting Document.” Attached is a template for the Proposed REMS that you should complete with concise, specific information (see Appendix A). Include information in the template that is specific to your proposed REMS for Pancrecarb (pancrelipase) Delayed-Release Capsules. Once FDA finds the content acceptable, we will include these documents as an attachment to the approval letter that includes the REMS.

The REMS Supporting Document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

Information needed for the assessments should include but may not be limited to:

- a. Patients’ understanding of the potential risks of Pancrecarb (pancrelipase) Delayed-Release Capsules.
- b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
- c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.

If you do not submit electronically, please send 5 copies of your proposed REMS as an amendment to your application. Prominently identify the proposed REMS submission with the following wording in bold capital letters at the top of the first page of the submission.

PROPOSED REMS FOR NDA 22-175

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

NDA 22-175 PROPOSED REMS-AMENDMENT

If you have any questions, please contact 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

Enclosures:

Appendix A: REMS Template

Appendix B: REMS Supporting Document Template

Appendix A: Medication Guide REMS Template

Application number TRADE NAME (DRUG NAME)

Class of Product as per label

Applicant name

Address

Contact Information

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

List the goals and objectives of the REMS.

II. REMS ELEMENTS:

A. Medication Guide

If a Medication Guide is included in the proposed REMS, include the following:

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

B. Timetable for Submission of Assessments

For products approved under an NDA or BLA, specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments shall be no less frequent than by 18 months, 3 years, and in the 7th year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Appendix B: REMS Supporting Document Template for Medication Guide REMS

This REMS Supporting Document should include the following listed sections 1 through 5. Include in section 3 the reason that the Medication Guide proposed to be included in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

TABLE OF CONTENTS

1. Background
2. Goals
3. Supporting Information on Proposed REMS Elements
 - a. Medication Guide
 - b. Timetable for Submission of Assessments of the REMS (for products approved under an NDA or BLA)
4. Information Needed for Assessments (for products approved under an NDA or BLA)
5. Other Relevant Information

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/s/

Julie Beitz
3/19/2009 11:57:21 AM



NDA 22-175

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) for Pancrecarb (pancrelipase) Capsules.

Refer also to our March 2, 2009 telephone conversation regarding the safety update requirements.

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all non-clinical and clinical studies 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 dropouts 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 a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

Please submit this information as soon as possible.

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

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Brian Strongin
3/2/2009 02:40:01 PM



NDA 22-175

INFORMATION REQUEST LETTER

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

Dear Dr. Sipos:

Please refer to your October 27, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pancrecarb (pancrelipase) Capsules.

We also refer to your submissions dated December 5, 2008 December 8, 2008 December 11, 2008 December 15, 2008.

We are reviewing the Pediatric Deferral in your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Please submit a partial pediatric waiver request for pediatric patients aged birth to less than 1 month.
2. Please amend your pediatric deferral to include pediatric patients aged 1 month to less than 2 years.
3. Please submit a pediatric plan. The pediatric plan has to include a general description of the studies to be conducted and a timeline that includes the date you will submit the protocol, the date the studies will begin, and the date the studies will be submitted. The pediatric plan does not have to be a full protocol.

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

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Brian Strongin
2/27/2009 11:51:59 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-175

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) Capsules.

We also refer to your submissions dated December 5, 2008, December 8, 2008, December 11, 2008, and December 15, 2008.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is **August 27, 2009**.

We are reviewing your application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team, and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by July 13, 2009.

Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

1. Under Section 2. Dosage and Administration of the proposed package insert (PI) in the second paragraph, you state that:



More detailed information is needed on *in vitro* stability study (No. RR-075) for the contents of Pancrecarb when mixed with applesauce in order to support the above statement. Please provide the experimental procedure, pH of applesauce tested, dissolution testing procedure, and analytical methodology. If you already submitted the needed information, please provide the location, i.e., the Module, Volume, and Page Numbers.

2. We have the following comments regarding the format of the proposed PI:

- I. Highlights of Prescribing Information

- a) Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- b) The preferred presentation of referencing in Highlights is the numerical identifier in parentheses [e.g., (1.1)] following the summarized labeling information, corresponding to the location of information in the FPI.
- c) Do not use the “R” symbol after the drug name in Highlights or the Table of Contents. You can use this symbol once upon first use in the FPI.
- d) 21 CFR 201.57(a)(6) requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

“Pancrecarb is a (name of class) indicated for (indication(s)).”

Please propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the highlights.

- e) A concise statement of each of the drug’s indications should be presented in bulleted format.

- f) Tabular format should be used to enhance accessibility of the Dosage and Administration information when there are different dosing regimens for different indications.
- g) Refer to 21 CFR 201.57(a)(11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).
- h) A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting [see 21 CFR 201.57(a)(11)].
- i) A revision date (i.e., Revised: month/year) must appear at the end of Highlights [see 21 CFR 201.57(a)(15)]. For a new NDA the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.

II. Full Prescribing Information (FPI)

- a) The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [*see Use in Specific Populations (8.4)*] not *See Pediatric Use (8.4)*. The cross reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print.
- b) Bullet the indications in the Indications and Usage section.
- c) Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline. Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format.

Please address the identified deficiencies/issues and re-submit labeling by March 13, 2009. This updated version of labeling will be used for further labeling discussions.

If you have not already done so, you must submit the 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>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We acknowledge receipt of your request for a deferral of pediatric studies for this application for pediatric patients aged birth (0 months) to 2 years.

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

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Division Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Donna Griebel

1/8/2009 06:40:46 PM



NDA 22-175

INFORMATION REQUEST LETTER

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

Dear Dr. Sipos:

Please refer to your 27 October 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pancrecarb (pancrelipase) Capsules.

We also refer to your submission dated 08 December 2008.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Please explain why you have modified the dissolution medium recommended by USP for buffer stage testing by adding olive oil substrate, casein substrate, and starch substrate to the phosphate buffer medium, and explain how these additional components affect the dissolution properties of the product. Please provide data to support your arguments.
2. At the conclusion of acid stage testing, a loss in enzyme activity of approximately (b) (4) is consistently observed in all samples. While USP allows for a 10% loss of drug substance during acid stage testing, observing such consistently high results is unusual, with most comparable products showing not more than 1 or 2 %, if any. The data for the current product suggest that the integrity of the enteric coating may be compromised during acid stage testing. Please provide an explanation for these results and explain whether (b) (4) was considered in developing this product.
3. With regard to the (b) (4) buffer stage dissolution limit in 30 minutes that you propose for lipase, please explain why this limit is much lower than the USP limit of 75% in 30 minutes. The justification that you have provided is not adequate. In your response you should include an explanation of why the lipase activity is consistently lower (by approximately (b) (4) in your dissolution data than the activity determined in assay of the capsules, and how it relates to the modification of the dissolution method and possibly coating integrity.

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

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Brian Strongin
12/18/2008 03:43:56 PM



NDA 22-175

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) for Pancrecarb (pancrelipase) Capsules, indicated for the treatment of exocrine pancreatic insufficiency.

We also refer to your submissions dated 20 June 2008 and 27 October 2008.

As discussed on 25 November 2008 between Digestive Care Inc. and The Division of Gastroenterology Products, the following filing issues have been identified:

1. Please submit an integrated safety dataset for all studies with the same column listings for each study. The columns should include: Study number, Unique patient ID number, Age, AE start date, AE end date, Dose at time of AE, Treatment group at time of AE, System Organ Class, Preferred Term, and Verbatim Term.
2. Your define pdf files do not define all fields in your studies. Please appropriately define all variables. (For example, in pivotal study 06-001, treatment sequence AB is not defined.)
3. The primary endpoint variable could not be identified in the datasets provided for all of the studies submitted with the NDA. Please revise the applicable datasets and define files so that the primary endpoint variable can be readily identified.
4. The NDA must contain an accurate comprehensive index. Please correct the Table of Contents such that all aspects of the NDA submission are available through one comprehensive table of contents.
5. Please amend your Debarment Certification, paragraph 2, sentence 1, by removing the phrase (b) (4)
6. We note you have identified this application as a 505(b)(1) application; however, Module 4 of this application includes a summary of published literature. Please see *FDA Guidance for Industry: Exocrine Pancreatic Insufficiency Drug Products-Submitting NDAs* and *FDA Guidance for Industry: Applications Covered by Section 505(b)(2)*. Please amend form 356h to identify the application type as a 505(b)(2) and submit the appropriate patent certifications.

As agreed upon by your firm during the above noted teleconference, please submit your response to these issues on or before 5 December 2008.

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

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Brian Strongin
12/3/2008 09:18:45 AM



NDA 22-175

NDA ACKNOWLEDGMENT

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

Dear Dr. Sipos:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Pancrecarb (pancrelipase) (b) (4) 8000, and 16000 USP units of lipase

Date of Application: October 27, 2008

Date of Receipt: October 27, 2008

Our Reference Number: NDA 22-175

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 26, 2008 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the 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>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

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

Sincerely,

{See appended electronic signature page}

Elizabeth A.S. Ford, RN
Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Elizabeth A Ford
11/10/2008 08:18:39 AM



NDA PRESUBMISSION ACKNOWLEDGEMENT

NDA 22-175

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

Dear Dr. Sipos:

We have received the first section of your New Drug Application (NDA) under the program for step-wise submission of sections of an NDA (section 506 of the Federal Food, Drug, and Cosmetic Act) for the following:

Name of Drug Product: Pancrecarb (pancrelipase) Capsules

Date of Submission: June 20, 2008

Date of Receipt: June 24, 2008

Our Reference Number: NDA 22-175

We will review this presubmission as resources permit. Presubmissions are not subject to a review clock or to a filing decision by FDA until the application is complete. Please cite the NDA number assigned to this application at the top of the first page of every communication concerning this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please call me, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Maureen Dewey, M.P.H.
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Maureen Dewey

7/16/2008 04:28:40 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 45,223

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

Dear Dr. Sipos:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PANCRECARB® (pancrelipase) Capsules.

We also refer to the September 4, 2007, correspondence, received September 5, 2007, requesting a meeting to discuss content and format requirements for NDA submission of a pancrelipase drug product, PANCRECARB®.

We also refer to the meeting between representatives of your firm and the FDA on October 31, 2007. The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-0845.

Sincerely,

(See appended electronic signature page)

Maureen Dewey, MPH
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: October 31, 2007
TIME: 11:00 AM – 12:00 PM
LOCATION: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room 1419
Silver Spring, MD 20993
APPLICATION: IND 45,223
DRUG NAME: Pancrecarb
TYPE OF MEETING: Type B Meeting
MEETING CHAIR: Anne Pariser, M.D.
MEETING RECORDER: Maureen Dewey, M.P.H.

FDA ATTENDEES:

Daniel A. Shames, M.D., Acting Director
Anne Pariser, M.D., Medical Team Leader
Virginia Elgin, M.D., Medical Reviewer
Gibbes Johnson, Ph.D., Supervisory Research Chemist
Wei Guo, Ph.D., Chemistry Reviewer
Sushanta Chakder, Ph.D., Acting Supervisory Pharmacologist
Tien-Mien Chen, Ph.D., Biopharmaceutics Reviewer
Sue Chih Lee, Ph.D., Biopharmaceutics Team Leader
Zei-Pao Huang, Regulatory Review Support Staff
Sonia Castillo, Ph.D., Biostatistical Reviewer
Maureen Dewey, M.P.H., Regulatory Project Manager
Jagjit Grewal, M.P.H., Regulatory Project Manager
Robin Nguyen, Regulatory Project Manager
Frances Fanbulleh, Pharm.D., Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Tibor Sipos, Ph.D., President and Chief Scientific Officer, Digestive Care, Inc.
William Humphries, M.S., Vice President, Marketing, Digestive Care, Inc.

(b) (4)

Jules Mitchel, Ph.D., Clinical/Regulatory Consultant, Target Health International, Inc.

MEETING OBJECTIVES:

The purpose of this meeting was to discuss the content and format requirements for NDA submission of a pancrelipase drug product, PANCRECARB®.

Question 1: DCI plans to comply with the content and format requirements for labeling of older prescription drug products as provided for in 21CFR201.80. *The Guidance for Industry: Labeling for Human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements, June 2004* provides exceptions for existing products on the market place. DCI believes that the PANCRECARB® drug product parallels the intent of these exceptions and that Physician Labeling Rule (PLR) label content and format according to the *Final Rule: Requirements on the Content and Format of Labeling for Human Prescription Drug and Biological Products (dated January 24, 2006; effective June 30, 2006)* would not be required for this product. Does the Division agree with this plan?

Response:

No. The Final Rule requires that prescription drug labeling for all NDAs submitted to FDA on or after June 30, 2006, be submitted in the PLR format. Should you require assistance with PLR, please email spl@fda.hhs.gov for individual assistance.

Question 2: For the purposes of the initial NDA submission, DCI is proposing to provide the draft labeling (package insert) in WORD and the annotated labeling in pdf format. Nearer to the completion of labeling negotiations with the Division, DCI would submit Structured Product Labeling (SPL) formatted labeling as an amendment to the NDA. Does the Division agree with this proposal?

Response:

You are required to submit to FDA prescribing and product information (i.e., the package insert or label) in SPL format at the time of initial NDA submission.

Please refer to Guidance for Industry: Providing Regulatory Submissions in Electronic Format — Content of Labeling (April 2005).

<http://www.fda.gov/cder/guidance/6719fnl.pdf>

Question 3: Will there be Class labeling developed and/or required for the pancreatic enzyme products? If so, would the Division be able to provide the required text to DCI at this time?

Response:

There are no current plans for Class labeling of the pancreatic enzyme products (PEPs); however, should Class labeling for the PEPs be developed, we will notify you at that time.

Question 4: The PANCRECARB® drug product has historically been formulated at 100% label-claimed lipase potency. The capsule fill weight is then adjusted in order to meet the specifications for lipase, amylase and protease content and to achieve the desired final dosage strength for (b) (4) MS-8, and MS-16. Adjusting the capsule fill weight to meet the specifications for lipase, amylase and protease content has historically resulted in a lipase potency in excess of the 100% label-claim. DCI has a large body of historical stability data, conducted under ICH conditions, on batches of drug product capsules produced in this manner.

DCI has specifically prepared three lots of each dosage strength of the PANCRECARB® drug product also formulated at 100% label-claimed lipase potency, but produced by adjusting the capsule fill weight based only on the 100% label-claimed lipase potency for (b) (4) MS-8, and

MS-16 capsules. These (b) (4) batches have been placed on stability study under ICH long term (25%C/60%RH) and accelerated (40%/75%RH) conditions. DCI will have approximately 6 months of real time stability data on all batches by the end of 2007, with 1 year data available on all batches by the end of June 2008. Will the Division accept the NDA for filing on the basis of 6 months of stability data under long term and accelerated conditions, for the (b) (4); (3 batches each of the (b) (4), MS-8 and MS-16) of drug product released at 100% label-claimed lipase potency, along with supportive historical stability data, and a commitment to provide periodic stability data updates during the NDA review cycle?

Response:

Yes. Historical data of capsules filled at overage can be considered as supporting data, but they cannot be used to substitute the stability data required to claim the product shelf life. Please submit these data and provide periodic stability data during the NDA review cycle.

Question 5: The PANCRECARB® drug product is available in (b) (4) MS-8, and MS-16)). The designations relate to the lipase activity of each dosage. All strengths have the same formulation (%w/w basis) of pancrelipase and inactive excipients, and the same manufacturing process. In order to satisfy the NDA Regional Section requirements for a blank master and completed batch record, DCI plans to include the current approved MS_16 blank master batch record along with the completed batch record for one lot of MS-16 (the specific batch used in the clinical study under Protocol 06-0001) in the PANCRECARB® NDA.

Does the Division agree with this plan?

Response:

We agree with the plan. However, the formulation and bead sizes of the (b) (4) MS-8 and MS-16 products are different. Please provide additional information to demonstrate the adequate control used in the manufacturing of (b) (4) MS-8, in addition to MS-16.

Question 6: DCI has submitted a final clinical protocol for the in vivo intraduodenal aspiration study to the Pancrecarb® IND#45,223 (Serial No. 035, dated January 29, 2007). The study, currently planned with 10 patients, is being conducted specifically to satisfy the requirement for a bioavailability study at the site of action (gastrointestinal tract) to support the NDA for PANCRECARB®. The first patient was enrolled at the end of April 2007. A second patient was enrolled in late June 2007. The next patient was enrolled in mid September 2007. DCI believes that the bioavailability data from these three patients is representative of the expected bioavailability for the remaining study group. DCI is requesting consideration by the Division relative to the diligence with which DCI is pursuing this difficult study, and its commitment to include the results of this study in the PANCRECARB® NDA. DCI is proposing to stop the study when at least 3 patients complete the study and to submit these data to fulfill the bioavailability study requirement.

Does the Division agree with this proposal?

Response:

We recommend that you submit a complete study report with your proposed ten patients at the time of NDA submission. It is unlikely that three patients will be sufficient to provide adequate power for your study.

Additional Discussion:

DCI stated that the NDA is ready to be submitted except for the bioavailability (BA) study. Two patients have been enrolled and have completed the BA study, and preliminary data for these two patients were presented at the meeting (see attachments).

FDA stated that it is DCI's decision whether to submit the NDA with these data (from only two patients from the ongoing BA study) or after completion of all ten proposed patients. The adequacy of the data from these two patients to support the NDA is a review issue, and will be determined upon review of the data during the NDA review cycle.

Question 7: In accordance with 21CFR314.50, an NDA is required to contain copies of individual case report forms for each patient who died during a clinical study or who did not complete the study because of an adverse event, whether believed to be drug related or not, including patients receiving reference drugs or placebo. This requirement may be waived by the FDA for specific studies if the case report forms are unnecessary for a proper review of the study.

Cystic Fibrosis (CF) is a complex chronic disease involving multiple organ systems where patients can be routinely hospitalized, experience disease-related adverse events and start/stop medications that may exacerbate their disease symptoms. CF patients comprised the majority of the populations included in the PANCRECARB® clinical studies that will be included in the NDA. All the safety information and final disposition of patients was captured on the study-specific Case Report Forms (CRFs) from each of the PANCRECARB® clinical studies and has been entered into a database. The complete data listings, including the safety and final disposition information for each patient in all the studies, will be included in the NDA.

Given the above, DCI proposes that no CRFs for patients enrolled in the PANCRECARB® clinical trials will be included in the PANCRECARB® NDA submission. The CRFs would be made available upon request during the NDA review, if needed.

Does the Division agree with this proposal and waive this requirement for the PANCRECARB® NDA submission?

Response:

No. We understand that cystic fibrosis (CF) is a complex disease with substantial morbidity and mortality; however, an independent and thorough review of the safety data by FDA Reviewers is an important and necessary component of any NDA review. We do not intend to waive this requirement. Therefore [per 21CFR 314.50(f)(2)], copies of individual CRFs for each patient who died during a clinical study, or who did not complete the study because of an adverse event must be included in your NDA

submission. Any additional CRFs needed to conduct a proper review of the application will need to be available upon request.

NDA FORMAT AND CONTENT PLAN

Question 8: All sections of the NDA will be prepared in accordance with the ICH Common Technical Document (CTD) format. The detailed Table of Contents for the PANCRECARB® NDA is provided in the Meeting Briefing Document. Does the Division agree with the proposed format and content plan for the PANCRECARB® NDA?

Response: In general, your proposed table of contents for the Pancrecarb NDA appears to be adequate, and is consistent with the ICH CTD format. However, we note the following deficiencies:

1. Under Module 5, section 5.3.7.1 Case Report Forms, you list the Location Folder/File Name as N/A. This is not acceptable (please see the response to Question 7, above).
2. Under Module 5, section 5.3.7.2 Clinical/Statistical Data, you have not provided a listing of the datasets you intend to submit. Thus, we cannot comment on the adequacy of this section.

Additional Discussion:

DCI stated that they intend to submit full data sets for all studies in the NDA. FDA clarified that we cannot comment on the adequacy of the data sets until the submission has been received.

Please refer to the Guidance of "Study Data Specification" for datasets folder and file structure. (<http://www.fda.gov/cder/regulatory/ersr/ectd.htm>)

Please note that a determination as to the adequacy of the NDA submission for filing can only be made after the submission has been received, and we have been given an opportunity to review its content.

Please be aware that eCTD will be the only Electronic Submission format acceptable to the Agency as of 2008. Using any other format requires a waiver. A waiver request should be sent to Esub@cderr.fda.gov.

ADDITIONAL COMMENTS:

1. It is unclear to us how Pancrecarb Delayed-Release capsules were administered to young children in your clinical trials. If the capsules were opened and the capsule contents sprinkled onto food, *in vitro* stability data for the product in this food should be provided in your NDA to support a labeling claim for administration of your product in this manner. Please clarify.

Additional Discussion:

DCI stated that the mode of administration of Pancrecarb to young children in the clinical studies (in applesauce) will be fully explained in the NDA. Stability data for Pancrecarb in applesauce will be submitted in the NDA.

2. Substitution of (b) (4) drug substance with the (b) (4) drug substance in the manufacturing of Pancrecarb would result in a different drug product. Due to the complex nature of these drug substances, it would not be possible to demonstrate physicochemical comparability, and comparability would have to be demonstrated by clinical data. Additionally, drug products manufactured using the (b) (4) drug substance would need to be added to your stability program.

Please clarify whether the pivotal clinical safety and efficacy studies performed in your clinical development program for Pancrecarb were performed with the product you intend to market.

Additional Discussion:

DCI clarified that all clinical studies were performed using the product manufactured with (b) (4) drug substance (DS). The sponsor further clarified that the product manufactured with (b) (4) DS is the product they intend to market.

FDA proposed that, subsequent to approval of the NDA, studies to support a substitution of (b) (4) DS with (b) (4) DS could be submitted as a manufacturing supplement with clinical data. The sponsor stated that at this time, their intention is to make the change from (b) (4) DS to (b) (4) DS after NDA approval. (b) (4)

FDA reiterated that given the complexity of the pancreatic enzyme products, it will not be possible to demonstrate comparability by physicochemical characterization alone. (b) (4)

3. Response to Pediatric Deferral Request:

Because of recent changes to PREA, we are not prepared to discuss your request for deferral during the meeting. However, we will respond to your request in writing at a later date.

Additional Discussion:

DCI requested a mechanism by which they can obtain comments on their proposed pediatric (less than two years of age) study design in a timely manner.

FDA stated that a response to this question will be provided in writing, and will be forthcoming.

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

/s/

Anne Pariser
11/6/2007 08:55:08 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 45,223

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

Dear Dr. Sipos:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Pancrecarb® (pancrelipase) ^{(b)(4)} MS-8 and MS-16.

We also refer to the meeting between representatives of your firm and the FDA on February 5, 2007. The purpose of the meeting was to discuss the chemistry and manufacturing issues to satisfy requirements for the NDA submission of Pancrecarb®.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Maureen Dewey, M.P.H.
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: February 5, 2007
TIME: 2:30 PM – 4:00 PM
LOCATION: White Oak Building 22, Conference Room 1419
APPLICATION: IND 45,223
DRUG NAME: PANCRECARB
TYPE OF MEETING: Type C
MEETING CHAIR: Wei Guo, Ph.D.
MEETING RECORDER: Maureen Dewey, MPH

FDA ATTENDEES:

Division of Gastroenterology Products

Brian E. Harvey, M.D., Ph.D., Director
Anne Pariser, M.D., Medical Team Leader
Virginia Elgin, M.D., Medical Reviewer
Maureen Dewey, MPH, Regulatory Project Manager

Division of Therapeutic Proteins

Barry Cherney, Ph.D., Deputy Director
Ennan Guan, Ph.D., Chemistry Reviewer
Gibbes Johnson, Ph.D., Supervisory Research Chemist
Wei Guo, Ph.D., Chemistry Reviewer

Division of Clinical Pharmacology III

Tapash Ghosh, Ph.D., Biopharmaceutics Reviewer, Acting Team Leader

EXTERNAL CONSTITUENT ATTENDEES:

Tibor Sipos, Ph.D., President and Chief Scientific Officer, Digestive Care, Inc.
William Humphries, M.S., Vice President, Marketing, Digestive Care, Inc.

(b) (4)

BACKGROUND:

On April 26, 1994, Digestive Care, Inc. (DCI) submitted IND 45,223 for Pancrecarb® indicated for the treatment of pancreatic enzyme insufficiency associated with cystic fibrosis.

On November 14, 2006, Digestive Care, Inc. requested a meeting to discuss clinical and chemistry and manufacturing issues to satisfy requirements for NDA submission. On December 21, 2006, the FDA received the background package. Preliminary responses were faxed on February 2, 2007.

MEETING OBJECTIVES:

Today's meeting objective is to discuss the chemistry and manufacturing issues to satisfy requirements for NDA submission of Pancrecarb®.

DISCUSSION POINTS:

Following introductions, DCI's questions from the December 21, 2006, background package were addressed. The format of these minutes provides for DCI's questions in regular typeface, followed by FDA's responses in **bolded** print, followed by the February 5, 2007 meeting discussion.

Question 1: Given that the patient dosing is based on lipase units, DCI believes that the clinical studies conducted with any one of the (b) (4) dosage strengths would support the safety and efficacy of all dosage strengths to satisfy the PANCRECARB NDA requirements. Does the Division agree?

Response:

(b) (4)

If you are unable to demonstrate comparability, you will need to provide clinical efficacy and safety data for those strengths that were not shown to be comparable.

Additional Discussion on 02/05/2007:

The sponsor stated that performance of the bioavailability study with two of the dosage strengths would lead to a substantial delay in the submission of the NDA. The sponsor had planned to submit the NDA in April 2007. Alternately, the sponsor is requesting to submit the NDA as planned in April 2007, with the clinical study report for the bioavailability study being submitted later in the year 2007 as an amendment to the NDA. The Division stated that the NDA should be complete at the time of initial submission, and should include all data that would be required for approval. Additional data submitted during

the review cycle may result in the extension of the PDUFA timeline, or submission of an incomplete application may result in an unfavorable review decision.

The sponsor stated that they feel they have adequate safety and efficacy data for all (b) (4) dosage strengths, and asked whether the bioavailability comparability results would be necessary for NDA approval. The Division stated it is up to the sponsor to make a determination as to the completeness of data in the NDA submission, and whether they have sufficient safety and efficacy data for all (b) (4) dosage strengths to support an NDA approval independent of the bioavailability comparability testing. The Division cannot comment on whether these data are adequate to support approval of all (b) (4) dosage strengths prior to review of the submission.

The sponsor stated that one of the major reasons for the delay in the bioavailability testing has been the availability of validated assays. The Division confirmed that for approval, assay validation must be consistent with ICH Guidelines at the time of approval. The Division agreed that assay validation can occur retrospectively; however, there are risks to this approach.

Question 2: Does the Division agree that the methodology and acceptance criteria employed for the particle sizes are adequate to control the quality of the product?

Response:

Describe the process controls installed, and demonstrate that the size of the microspheres is within specification after the (b) (4) process.

Question 3.a Does the Division agree with the definition of specific activity as used by DCI?

Response:

Yes.

Question 3.b Does the Division agree with the definition of "optimal conditions" (i.e., temperature, pH, natural substrates, ionic concentration, etc.) as defined in the current DCI enzyme assay methods?

Response:

Optimal conditions should be determined in your new assay development.

Additional Discussion on 02/05/2007:

The Division clarified the response to state that data must be provided for the assays being tested to demonstrate that testing was performed under "optimal conditions" for that assay. "Optimal conditions" must be determined empirically.

Question 3.c Does the Division agree that it is imperative to use a natural substrate to determine the enzymatic activity of the proteases to correlate with the naturally occurring digestive processes in the human gastrointestinal tract?

Response:

Yes.

Question 3.d Should the calculation of enzyme potency be based on initial slope of the reaction vs. fixed time assay?

Response:

Yes. Initial velocity should be used to measure the enzyme activity.

Question 3.e Does the Division agree that the USP Pancrelipase Reference Standard or an "in-house" prepared Pancrelipase Reference Standard would satisfy the requirements for the demonstration that other components in the drug product; i.e., excipients, do not interfere with the enzyme assays?

Response:

No. In order to demonstrate that the other components of the drug substance and product do not interfere with the assay method, relatively pure lipase, or USP standard should be spiked into your drug substance and product. The increased activity should be proportional to the amount of enzyme activity added and measure independently.

Question 3.f Does the Division agree that it will be imperative to continue to use the currently employed enzyme method for lipase activity in order to maintain continuity of this critical potency determination?

Response:

Yes. However, the requirements for the enzymatic methods for Lipase, Amylase, and Protease activities as noted in the minutes of the teleconference held on September 11, 2006 must be provided in your NDA submission.

Question 4: If the Division will accept the NDA for filing based on the currently available PANCRECARB[®] drug product stability data on batches initially released at up to (b) (4) of lipase activity?

Response:

No. Your filling target should be (b) (4) of the label claim for lipase activity at the product release. Overage to compensate for shelf life stability is not acceptable (see Guidance for Industry, Exocrine Pancreatic Insufficiency Drug Products, Section III. D. Overages, p.4 and p.5).¹

¹ U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for Industry Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs. April 2006. <www.fda.gov/cder/guidance/6275f1.pdf>.

Additional Discussion on 02/05/2007:

The sponsor noted that there have been problems with their dissolution testing methods. The sponsor requested a waiver from conducting dissolution testing, as they feel dissolution testing is not an adequate reflection of the quality of the product, but rather a problem with the test itself. The Division stated that dissolution testing is an important part of quality control testing, and the sponsor will need to propose an alternative method of quality control testing. The Division agreed to review any alternative methods being proposed by the sponsor, but cannot make a determination as to the adequacy of the alternative testing method prior to review of the sponsor's proposal.

Question 5: Does the Division agree that full shelf-life stability data are not required from 3 consecutive manufacturing batches for (b) (4) dosage strengths (b) (4), MS-8 and MS-16), or for 3 lots of all bottling configurations (i.e., 100 and 250 capsules/bottle)?

Response:

No. Stability data from all (b) (4) dosage strengths of the drug product filled at (b) (4) label claim should be provided in your NDA submission.

Additional Discussion on 02/05/2007:

The Division clarified that the same product in two different bottles will not be necessary for meeting the requirements.

The sponsor will request a teleconference to discuss the specifics of the stability of the product through the Regulatory Project Manager (RPM) at a future time.

Question 6: Does the Division agree with both the proposed (b) (4) plan and the protocol for annual product stability testing?

Response:

The (b) (4) approach can be used after two years, after the stability of product in all five packages is established. The new enzymatic assays should be used to assess the activity of lipase, amylase, and protease activities.

Question 7: Does the Division agree that stability studies conducted on the commercial product support the assignment of the same shelf-life to the (b) (4) for each dosage strength do not need to be part of the routine annual stability program?

Response:

Yes.

Question 8: Does the Division agree that photo stability studies, and additional stress stability studies on the PANCRECARB® drug product are not required to support the PANCRECARB® NDA?

Response:

Additional stability data at storage conditions, at accelerated conditions, and under stress conditions should be provided using product filled at (b) (4) label claim. Photo stability data should be provided or an appropriate warning should be clearly stated on the label to advise the consumers.

Question 9: Does the Division agree that the correct name for the product would be PANCRECARB (pancrelipase) Capsules, containing enteric-coated buffered microspheres?

Response:

This question will be addressed at the time of NDA review.

Question 10: The trade name PANCRECARB was filed to the US Patent and Trademark Office by Digestive Care, Inc. on June 19, 1995, and registered on March 11, 1997. PANCRECARB Capsules have always been available only by prescription under this trade name since 1995. Will a proposed proprietary name application be required to be submitted and approved by the agency for the PANCRECARB trade name?

Response:

This question will be addressed at the time of NDA review.

Question 11: Does the Division agree that the PANCRECARB® (pancrelipase) NDA would qualify for a categorical exclusion from the requirements to prepare an Environmental Assessment?

Response:

Yes.

Question 12: Would the Division accept the (b) (4) DMF (b) (4) cross reference letter in full satisfaction of the drug substance portions of Module 2 and Module 3 of the PANCRECARB® NDA to enable filing of the PANCRECARB® NDA?

Response:

Yes. DMF (b) (4) will be reviewed if it is referenced properly. The decision regarding the acceptability of the information in the DMF will be made after review of the information.

Additional Discussion on 02/05/2007:

The Division clarified that "referenced properly" means that the sponsor should state in the submission that the DMF is referenced, and provide a Letter of Authorization from the DMF holder.

Question 13: Would the Division accept the PANCRECARB[®] NDA for filing if the (b) (4) DMF (b) (4) updates regarding characterization of the pancrelipase drug substance, chemical characterization and validation of the enzyme assays, and the viral clearance information were to be submitted during the review cycle of the DCI PANCRECARB[®] NDA submission?

Response:

Some additional, limited updates of the information may be made to DMF (b) (4) but should be submitted early in the review cycle to allow adequate time for review.

1. Part 6B: Questions submitted by DCI on behalf of (b) (4)

A. Animal Sourcing:

Question 1: Does FDA agree that obtaining pancreas glands from (b) (4) with the sourcing controls as described in the Overall Summary, (see Attachment 8) is an acceptable practice for the preparation of the Pancreatin/Pancrelipase drug substance?

Response:

Yes.

B. Reversed Phase HPLC Methodology:

Question 2: Does FDA agree that the proposed RP-HPLC Method is suitable for identification and for quantitation of the (b) (4) peak for Pancreatin API release?

Response:

Yes. Please provide quantitative characterization of (b) (4) lipase, (b) (4) and amylase.

Additional Discussion on 02/05/2007:

The (b) (4) representative clarified that (b) (4) has finished the characterization studies for 1208 and 1206. A technical report for 1208 has been submitted to the DMF, and the report for 1206 will be submitted as soon as it is available.

(b) (4) will provide additional characterization data early in 2008. Ratios of the peaks can be provided, but quantification of the peaks is difficult due to the number of proteins in each peak. (b) (4) The Division stated that (b) (4) should submit these data for review as an update to the DMF. (b) (4) stated that the annual report usually is submitted in October, but they will submit it earlier given the anticipated timelines for this NDA.

Question 3: Does FDA agree to allow (b) (4) to obtain release and stability data for the (b) (4) content over the course of one year in advance of setting numerical release and stability specifications in order to allow the capture of release and stability data from a wide variety of the porcine starting raw material?

Response:

Yes. However, the results of these studies must be submitted to DMF and referenced in the NDA.

C. Biological Assay Methodology:

Question 4: Does FDA agree to allow (b) (4) to assess the data from the biological characterization studies currently in progress for the seven activity assays and then to select the appropriate assays for use in release and stability applications?

Response:

Yes. However, the results of these studies must be submitted to DMF and referenced in the NDA.

Question 5: Does FDA agree to allow (b) (4) to obtain release and stability data for the selected activity assays over the course of one year in advance of setting numerical release and stability specifications in order to allow the capture of release and stability data from a wide variety of the porcine starting raw material?

Response:

Yes. However, the results of these studies must be submitted to DMF and referenced in the NDA.

D. Viral Risk Management (ICH Q9):

Question 6: Does FDA agree that, as recommended in ICH Q5A, periodic testing of the finished API for presence of certain identified human pathogenic viruses (SVDV, Hep-E, and EMCV) may be an acceptable measure of safety from the risk of adventitious viruses?

Response:

No, you have failed to provide sufficient information to allow us to conclude that your proposed program provides an acceptable measure of safety from the risk of adventitious viruses. To address our concerns you should provide a thorough risk assessment (see Guidance for

Industry Q9 Quality Risk Management²) that includes potential infectious agents, their zoonotic potential, estimation of viral loads, and a risk management strategy (animal disease surveillance/prevention, raw material management, viral clearance capacity, and monitoring). However, we believe that due to incomplete knowledge regarding the risks from adventitious agents, and the heterogeneity of source animals, routine rather than periodic testing of the finished API for presence of certain potentially human pathogenic viruses is more appropriate.

To help guide you in your evaluation of viral safety, detailed comments regarding viral safety studies are also provided.

1. In order to conclude that virus validation studies are sufficient to demonstrate that the manufacturing process leads to an effective inactivation of viruses, one has to understand the input viral load. Thus, you should evaluate the starting material per ICH Q5A "A Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin".³ Screening of the starting material should focus on adventitious viruses that might be found in porcine tissue that have potential as human pathogens, and can be inactivated by the manufacturing process. Please include a justification for the viruses chosen (e.g. from your risk assessment). If it is infeasible to evaluate starting material, it may be appropriate to monitor different manufacturing steps.

Additional Discussions on 02/05/2007:

(b) (4) has contracted with a Virology expert, who will be assisting (b) (4) in drafting an overall risk assessment plan and plans for future studies. The Division stated that a thorough risk assessment plan is expected, and an appropriate level of monitoring is to be based on that assessment. It is likely that more information will be requested early in the review based on knowledge available at that time, and that these requests may be decreased over time as more is learned about the inherent risks. A follow-up meeting to discuss risk assessment was suggested given the importance of this assessment to the overall clinical development program, and to the assessment of risks to patient health. The sponsor stated that (b) (4) cannot request a meeting separately and that a joint meeting will be requested in the future.

2. Given the intended route of administration, we believe that for enveloped viruses, demonstration of acceptable clearance based on viral loads might be

² 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). Guidance for Industry Q9 Quality Risk Management, June 2006, <http://www.fda.gov/cder/guidance/index.htm>

³ 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). Guidance for Industry, Q5A Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin, June 2006.

sufficient (e.g. in lieu routine monitoring) but we encourage you to assess all process steps (b) (4) that could reduce risks associated with these adventitious viruses.

3. For non-enveloped virus, we believe it is necessary to evaluate the (b) (4) step or additional viral clearance steps for their capacities to inactivate viruses. These studies should use relevant models based on your risk assessments, and reflect your manufacturing process and control ranges. Routine testing for certain identified human pathogenic viruses may be appropriate.

Although porcine parvovirus (PPV) has not been shown to be infectious to humans, the ability of parvoviruses to alter their host range and pathogenic properties with relatively minor genetic change is of concern, particularly because of the potential PPV viral loads in your final product, and the fact that your manufacturing process is unlikely to clear PPV. We suggest routine monitoring for PPV.

Additional Discussion on 02/05/2007:

DCI will request a joint meeting to discuss the routine testing with the Division of Therapeutic Proteins through the RPM.

ACTION ITEMS:

- The sponsor will request a teleconference to discuss the specifics about the stability of the product through the RPM at a future time.
- DCI will request a joint meeting to discuss the viral risk assessment plan and routine testing with the Division of Therapeutic Proteins through the RPM.

ATTACHMENTS/HANDOUTS:

(b) (4) Letter of Authorization

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this page is the manifestation of the electronic signature.**

/s/

Maureen Dewey
2/13/2007 01:59:35 PM

Wei Guo
2/13/2007 02:26:37 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 45.223

Digestive Care, Incorporated
Attention: Glen Park, PharmD.
Senior Director, Clinical and Regulatory Affairs
261 Madison Avenue, 24th Floor
New York, NY 10016

Dear Dr. Park:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PANCRECARB[®] (pancrelipase) Capsules.

We also refer to the teleconference between representatives of your firm and the FDA on September 11, 2006. The purpose of the meeting was to discuss clinical and non-clinical issues to satisfy requirements for NDA submission of a pancrelipase drug product, PANCRECARB[®].

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Maureen Dewey, Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Maureen Dewey
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation 3
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF TELECONFERENCE MEETING MINUTES

MEETING DATE: September 11, 2006
TIME: 1:00 pm – 2:00 pm
APPLICATION: IND 45,223
DRUG NAME: Pancrecarb®
TYPE OF MEETING: Type C
CALL IN NUMBER: [REDACTED] (b) (4)

MEETING CHAIR: Ruyi He

MEETING RECORDER: Maureen Dewey

FDA ATTENDEES:

Joyce Korvick, M.D., M.P.H., Deputy Director
Ruyi He, M.D., Medical Team Leader
Fathia Gibril, M.D., Medical Reviewer
Anne Pariser, M.D., Medical Team Leader
Virginia Elgin, M.D., Medical Reviewer
Ethan Hausman, M.D., Medical Reviewer
Joanna Ku, M.D., Medical Reviewer
Jasti Choudary, Ph.D., Supervisory Pharmacologist
Wei Guo, Ph.D., Chemistry Reviewer
Suliman Al-Fayoumi, Ph.D., Biopharmaceutics Reviewer
Maureen Dewey, Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Tibor Sipos, Ph.D., President and Chief Scientific Officer, Digestive Care, Inc.
William Humphries, M.S., V.P. Marketing Digestive Care, Inc.

[REDACTED] (b) (4)

Jules Mitchel, Ph.D., Regulatory Consultant, Target Health Inc.
Colleen Johnson, MS, DABT, Toxicology Consultant, Target Health Inc.
Glen Park, PharmD, Senior Director, Clinical and Regulatory Affairs, Target Health Inc.

BACKGROUND:

On April 26, 1994, Digestive Care, Inc. submitted IND 45,223 for Pancrecarb® for the treatment of pancreatic enzyme insufficiency associated with cystic fibrosis.
On December 30, 2004, Digestive Care, Inc. submitted a meeting request for a Type B,

pre-NDA meeting for Pancrecarb[®]. On January 12, 2005, Digestive Care, Inc. submitted a cross reference letter authorizing Target Health, Inc to represent Digestive Care, Inc. concerning IND 45,223. On May 23, 2005, the sponsor submitted background information and questions for the meeting. Responses to the questions posed by the sponsor were faxed to the sponsor on June 21, 2005. On June 23, 2005 a Type B Meeting was held between the sponsor and the agency.

On August 23, 2005, Digestive Care, Inc. (DCI) submitted a Meeting Request and on September 21, 2005, a subsequent background package which contained specific questions as a follow-up to their June 23, 2005 meeting with FDA. Pre-meeting responses were faxed to DCI's regulatory representative on October 18, 2005 to provide focus for the meeting discussion. On October 19, 2005, a meeting to discuss the adequacy of DCI's proposed approach to characterizing pancrelipase for Pancrecarb[®] and biological activity methodology for drug substance and drug product release was held.

On June 29, 2006, Digestive Care, Inc. submitted a meeting request for a Type B Meeting. A Type C Meeting was granted on July 12, 2006. The meeting package was received August 14, 2006. Preliminary responses to the meeting questions were faxed to the sponsor on September 8, 2006. On September 11, 2006, the agency received a document containing clarifications to the preliminary responses and a request to change the face to face meeting to a teleconference.

MEETING OBJECTIVES:

The purpose of today's meeting is to clarify and discuss FDA's September 8, 2006 responses as needed.

Discussion Points: Following introductions, DCI's questions from the August 14, 2006 background package were addressed. The format of these minutes provides for DCI's questions in regular typeface, followed by FDA's responses in **bolded** print, followed by the September 11, 2006 meeting discussion in *italic and bolded* print.

Question 1: Based on the minutes of the July 23, 2005 pre-NDA meeting, DCI prepared a review of the toxicology data available on the excipients present in PANCRECARB[®]. This review has been included in this submission and DCI plans to submit a copy of each reference cited as per the request of the FDA in the July 11, 2006 letter. DCI believes that this review is comprehensive, addresses the issues raised by the Agency, and satisfies the requirements for the nonclinical pharmacology and toxicology sections of the PANCRECARB[®] NDA. Does the Agency agree?

Response:

Yes, provided that you follow the advice given in the Division's letter dated July 11, 2006 requesting comprehensive summaries of the details of chronic toxicology studies. (Please refer to response #1. in the above mentioned letter).

Comments to Question 1: All of the excipients used in PANCRECARB® are USP/NF compendial items, and some are also GRAS and/or present at levels previously found by the Division to be acceptable. A comprehensive summary of the safety and toxicology information for each of the excipients has been prepared and previously supplied to the Agency. In order to prepare the summary, DCI relied upon information from suppliers of the excipients and access to published literature and available information in the public domain. To the extent possible, DCI has summarized the available information from these sources which oftentimes contain limited information on the details of the study designs and outcomes.

DCI has not conducted any chronic toxicity studies on PANCRECARB® and does not have access to any chronic toxicology information on the pancrelipase active substance. A report on an acute oral toxicity study in rats performed on PANCRECARB® has been previously submitted.

Given this scenario, DCI is requesting clarification of what the Division is referring to by the request for "comprehensive summaries of the details of chronic toxicology studies".

Additional Discussion:

The sponsor will revisit the references including updated toxicity exposure assessments and provide additional information where possible.

Question 2: Ursodiol (b) (4) is included in the formulation (b) (4) components of the pancrelipase. DCI believes that ursodiol is appropriately designated as an inactive ingredient, and is considered safe for use at the levels present in the drug product. Does the Agency agree?

Response:

Yes.

Question 3: Sodium bicarbonate/carbonate are included in the PANCRECARB® formulation as inactive ingredients (b) (4). Does the Agency agree?

Response:

Yes.

Question 4: DCI believes that information to be gained from *in vivo* bioavailability data using aspirates from the stomach and duodenum would not contribute meaningful information to our knowledge of intraluminal digestion of a meal and the resolution of steatorrhea and therefore it will not be required to support the NDA for PANCRECARB®. Does the Agency agree?

Response:

An *in vivo* intraduodenal aspiration study is required to support an NDA submission for exocrine pancreatic insufficiency drug products. While the findings of an *in vivo* intraduodenal aspiration study do not necessarily correlate with the

clinical outcome, the study serves as critical proof of concept in support of the *in vivo* activity of the drug product. Please refer to the *Guidance for Industry Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs*. The Guidance states that “an NDA must meet the requirements in 21 CFR 314.50 for human pharmacokinetic and bioavailability information.”

Comments to Question 4: The Division has confirmed that an *in vivo* intraduodenal aspiration study is required to support the NDA for PANCRECARB[®], and that the purpose of this study is to serve as critical proof of concept to support the *in vivo* activity of the drug product. In order to complete the work to satisfy this NDA requirement, DCI is requesting further clarification on the details of such a study; e.g.:

- required number of subjects,
- acceptability of adult CF patients and chronic pancreatitis patients for the study population,
- study design considerations for managing inter- and intra-patient variability,
- intubation methodology to be employed,
- bioanalytical methodology for analysis of the gastric and duodenal aspirates to be employed,
- what are the specific parameters to be measured for the *in vivo* activity (bioavailability), other than lipase, amylase and protease activities, that are required to be studied under fasting and standard meal simulation,
- are there any surrogate biomarkers that might be employed to measure *in vivo* activity (i.e., appearance of a marker in the blood that coincides with the release of the marker and the release of the enzymes from the enteric-coated microspheres).
- DCI plans to allocate significant company resources, and use its best efforts to complete the required study for inclusion in the NDA submission. However, given the anticipated amount of time needed to prepare for and complete such a study, would the Division accept the NDA for filing without the results of this study, and further consider the submission of the final results of the study as a post-approval commitment?

Additional Discussion:

- ***There is no specific number of subjects recommended in the Guidance, however, the study must be adequately powered to detect a meaningful difference from baseline.***
- ***We recommend that you use patients with CF or patients with chronic pancreatitis rather than healthy volunteers.***
- ***In your study, you do not need to consider intra-patient variability. The study should be conducted under fed conditions, it is not necessary to have a “fasting” arm.***
- ***There is no particular intubation methodology that we recommend.***
- ***The bioanalytical methodology for analysis of the gastric and duodenal aspirates should be adequately validated.***
- ***When measuring specific parameters for the *in vivo* bioavailability, peak levels of the entity to be measured and area under the curve are the most important parameters to consider.***

- *We recommend that the aspiration would be taken from the duodenal section of the small intestine.*
- *There are no systemic surrogate biomarkers that have previously been employed.*
- *We recommend you submit the results of the study at the time of NDA submission.*

Question 5: DCI believes that the results of the eight clinical studies conducted with over 200 patients are sufficient to satisfy the submission requirements for the PANCRECARB[®] NDA. Does the Agency agree?

Response:

The proposed clinical data may be sufficient for the submission of an NDA. However, the adequacy of the clinical data to support approval of an NDA is a review issue.

Additional Discussion:

The sponsor agreed to re-submit this question in the future when they have established the study and have a better understanding of the time line for delivery of the study. We believe this is important information to submit to the NDA.

Question 6: DCI believes that the current body of clinical data generated with the (b) (4) MS-8, and MS-16 PANCRECARB[®] drug product supports the submission requirements for inclusion of all (b) (4) dosage strengths in the PANCRECARB[®] NDA. Does the Agency agree?

Response:

You may submit the clinical data that include all (b) (4) dosage strengths under an NDA. However, the final determination of appropriate dosing is data dependent.

The enzymatic methods for Lipase, Amylase, and Protease activities in drug substance and product release testing and stability studies must meet the following requirements: (i) utilize specific activity measurements to determine lipase, amylase and protease potencies (ii) the measurements must be performed under optimal conditions and use a substrate that has been characterized with regard to identity and purity (iii) the generation of product must be linear with respect to time and (iv) the other components in the drug substance and product must not interfere with the assay. A demonstration that the assays meet these requirements must be provided in the NDA submission.

Please describe the method to measure the particle size of the microsphere product and define the acceptance criteria for particle size.

Comments to Question 6: DCI presented formulation and particle size information for the (b) (4) MS-8 and MS-16 dosage strengths in the meeting briefing document, and

indicated that the clinical data were generated with drug product covering the same pharmaceutical particulars.

The Division replied that “you may submit the clinical data that include all (b) (4) dosage strengths under an NDA”. DCI is interpreting the Division’s statement to mean that there is no need to run additional clinical studies with individual dosage strengths. Is this interpretation correct?

Additional Discussion:

Yes, at this time, we do not require additional studies.

Comment to Question 6 continued: The clinical practice of pancreatic enzyme replacement with PANCRECARB[®], like all other pancreatic insufficiency drug products, is determined based on lipase units. The lipase dose is determined based on the individual patient’s level of pancreatic insufficiency and supervised by a physician. The (b) (4) dosage strengths of PANCRECARB[®] ((b) (4) MS-8 and MS-16) allow for titration of lipase doses to meet the individual patient’s needs. Given this information, DCI is unclear as to the meaning and would like further clarification on the Division’s comment that “the final determination of appropriate dosing is data dependent”.

DCI would request to defer discussion of the Division’s comments regarding the microsphere particle size measurement methodology and acceptance criteria, as well as the enzymatic method requirements for lipase, amylase and protease, for a future meeting to be requested specifically focused on CMC issues.

Question 7: DCI believes that the total combined information from the clinical studies conducted with PANCRECARB[®] would satisfy the pediatric study requirements for the PANCRECARB[®] NDA. Does the Agency agree?

Response:

Your proposal appears acceptable for ages 2-18. However, since cystic fibrosis (CF) affects all pediatric age groups, we recommend you conduct studies to evaluate safety and efficacy of the product in pediatric subjects aged ≤ 2 years using an age-appropriate formulation in the future.

Comments to Question 7: The Division agreed that the total combined information from the clinical studies conducted with PANCRECARB[®] would satisfy the pediatric study requirements for the PANCRECARB[®] NDA, specifically for the ages 2-18 years.

DCI would intend to request a deferral of pediatric study requirements for ages <2 years (with an age appropriate formulation) at the time of submission of the PANCRECARB[®] NDA. Does the Division agree with this plan?

Additional Discussion:

Yes, we would consider such a request. Please provide the rationale for your request in writing.

Currently, PANCRECARB[®] capsules are being opened and the microspheres sprinkled into applesauce or some other food for infants and toddlers. Does the Division consider this an “age appropriate formulation”?

Additional Discussion:

We would consider this as a feasible method, however, we will review your rationale for the “age appropriate formulation” at the time of your NDA submission. Please include activity in pediatric patients as well as stability information.

Pancrelipase appears on the *LIST OF APPROVED DRUGS FOR WHICH ADDITIONAL PEDIATRIC INFORMATION MAY PRODUCE HEALTH BENEFITS IN THE PEDIATRIC POPULATION*. If DCI were to pursue and receive a Written Request from the Division for conducting a study in pediatric subjects ages <2 years, would there be a possibility for DCI to receive the additional 6 months exclusivity if the study was successfully completed?

Additional Discussion:

We will discuss the Written Request with you once after you have submitted your Pediatric Proposed Study Request (PPSR).

Question 8: Currently, there are no marketed exocrine pancreatic insufficiency drug products with an approved NDA. Based on this unmet medical need, DCI would plan to request for Priority Review upon submission of the PANCRECARB[®] NDA. Under what circumstances would the Division NOT consider a Priority Review for the PANCRECARB[®] NDA?

Response:

A priority review may not be considered if another pancreatic enzyme product exists as an approved product, unless you can demonstrate advantages compared to the approved product at the time of your NDA submission.

Comments to Question 8: DCI is requesting further clarification on this point. The Cotazym NDA was approved in 1996. Is the Division indicating that, although this product was withdrawn from the market in 2002, it is still considered an “approved NDA” for the purposes of the ability to grant a Priority Review for an NDA yet to be submitted for another exocrine pancreatic insufficiency drug product?

If so, would the Division consider accepting a request for Priority Review upon submission of the PANCRECARB[®] NDA based on a literature review demonstrating the advantages of enteric-coated pancreatic enzyme microspheres over pancrelipase powder-filled capsules which was the Cotazym dosage form?

Additional Discussion:

See response to Question 8 above.

Alternatively, could the body of pediatric clinical data available for PANCRECARB® be used as the basis for a request for Priority Review?

Additional Discussion:

No.

DCI is also requesting if the Division would explain how marketing exclusivity will be handled for the approval of exocrine pancreatic insufficiency drug products.

Additional Discussion:

Please request a meeting to discuss marketing exclusivity after you have submitted your NDA.

Additional Question:

Is a ^{(b) (4)} overage allowed?

Additional Discussion:

No, there is no allowance for overage. Please refer to the Guidance for Industry Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs (III. Chemistry, Manufacturing, and Controls Section of the Application, Subsection D. Overage)

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

/s/

Ruyi He
9/29/2006 11:07:33 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 45,223

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

Dear Dr. Sipos:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PANCRECARB®.

We also refer to the pre-NDA meeting between representatives of your firm and the FDA on June 23, 2005.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-9333.

Sincerely,

{See appended electronic signature page}

Monika Houstoun, Pharm.D.
Regulatory Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

Memorandum of Meeting Minutes

Meeting Date: June 23, 2005
Meeting Time: 1:00 - 2:30 p.m.
Meeting Location: Conference Room C, Parklawn Building, Rockville, MD

Application Number: IND 45,223
Drug Name: Pancrecarb
Type of Meeting: Type B
Meeting Chair: Ruyi He, M.D.
Meeting Recorder: Monika Houstoun, Pharm.D.

BETWEEN:

Digestive Care, Incorporated

Tibor Sipos, Ph.D, President Digestive Care Inc. (DCI), Bethlehem, PA

(b) (4)

William T. Humphries, MS, V.P. of Marketing Digestive Care, Inc. (DCI)

(b) (4)

Glen Park, Pharm.D., Sr Director, Clinical and Regulatory Affairs, Target Health Inc.,
New York, NY

Colleen Johnson, Toxicology Consultant, Target Health Inc., New York, NY

Jules T. Mitchel, Ph.D., Regulatory Affairs, Target Health Inc., New York, NY

AND

Division of Gastrointestinal and Coagulation Drug Products (DGC DP), HFD-180

Ruyi He, M.D., Medical Team Leader

Fathia Gibril, M.D., Medical Officer

Jasti Choudary, Ph.D., Supervisory Pharmacologist

Ali Al-Hakim, Ph.D., Chemistry Reviewer

Monika Houstoun, Pharm.D., Regulatory Project Manager

Office of Clinical Pharmacology and Biopharmaceutics (OCPB), HFD-870

Suresh Doddapaneni, Ph.D., Biopharmaceutics Team Leader

Division of Biometrics II (HFD-715)

Stella Grosser, Ph.D., Statistical Team Leader

Office of New Drug Chemistry II, HFD-820

Blair Fraser, Ph.D., Deputy Director

PURPOSE:

To discuss the drug development program for Pancrecarb and requirements for NDA submission.

BACKGROUND:

On April 26, 1994, Digestive Care, Incorporated submitted IND 45,223 for Pancrecarb for the treatment of pancreatic enzyme insufficiency associated with cystic fibrosis.

On December 30, 2004, Digestive Care, Incorporated submitted a meeting request for a Type B, pre-NDA meeting for Pancrecarb.

On January 12, 2005, Digestive Care, Incorporated submitted a cross reference letter authorizing Target Health, Inc to represent Digestive Care, Inc. concerning IND 45,223.

On May 23, 2005, the sponsor submitted background information and questions for the meeting.

Responses to the questions posed by the sponsor were faxed to the sponsor on June 21, 2005.

DISCUSSION:

Responses to the questions posed by the sponsor.

Questions

1. Does FDA agree that the toxicology summary of the excipients is adequate to support the toxicology requirements of the NDA?

FDA Response:

No. The toxicology summary of the excipients is not adequate. The summary should be comprehensive and provide assessment of each excipient in relation to the total daily dose and toxicological findings. The NDA should also provide copies of the references. Please explain the role of ursodiol in your formulation. Provide justification for inclusion of this pharmacologically active component. Additionally, explain the roles of sodium carbonate and sodium bicarbonate in light of this being an enteric coated product.

Sponsor will provide comprehensive assessment of each excipient and a rationale. (b) (4)

Sponsor will provide a detailed rationale including safety information for both ursodiol and bicarbonate.

2. USP specifications for lipase are NLT 90% and NMT 165%. We normally compound at (b) (4) of label. What is the position of the Agency on the upper limit of lipase potency?

FDA Response:

The finished product should be formulated to be (b) (4) of label claim potency for lipase, the other enzyme contents will vary within justified limits.

3. Currently we are testing the drug substance for identity by employing the IR/KBr spectrophotometric method and we use the USP test method for lipase, amylase and protease potency determinations. Are these test methods acceptable for the acceptance of the drug substance?

FDA Response:

The USP monograph specifications and methods are considered inadequate. More appropriate specifications based on adequate characterization are needed. The DMF related to the drug substance need to be updated, it is Not Adequate at this time. The drug substance should be adequately characterized using appropriate chemical, physical and biological testing. Batch to Batch consistency with respect to chemical identity, biological activity for different enzymes including specific activity, identity and purity level should be demonstrated.

4. Pancrelipase comes in two different strengths. (b) (4) 1206 (b) (4) and (b) (4) 1208 (b) (4)

Is this acceptable?

FDA Response:

Yes, it could be acceptable.

5. Two research reports (RR-058 and RR-059) were prepared to compare USP procedure to DCI TM-6013 for the assay of lipase activity in pancrelipase containing products. The proposed methods are modifications of the current USP test for product release. Is this method and validation acceptable to the Agency?

FDA Response:

The USP Assay is considered inadequate at this time, please refer to DMF (b) (4) that covers the drug substance information. Please convey this information to DMF holder of DMF (b) (4)

6. The proposed dissolution specification, TM6007 (b) (4), is also different from current USP specifications for product release. Is this acceptable to the agency?

FDA Response:

No. A suitable validated method needs to be developed. The characterization and analytical methods for Assays need to have been updated and considered adequate before this can be evaluated.

Sponsor will do additional developmental work.

7. (b) (4) in the finished product is NMT (b) (4). Due to the (b) (4) in previously tested samples, these (b) (4) are no longer tested in the finished product. Is this acceptable?

FDA Response:

No. The proposed release specification should include (b) (4). The specification should reflect manufacturing capability.

Sponsor agrees.

8. Is the stability program described adequate for the NDA submission? What is the minimum stability requirement for (b) (4) strengths of pancrelipase in (b) (4) containers?

FDA Response:

Please clarify why (b) (4) different containers are needed (b) (4).

In general, a minimum of 12 months of stability data for each strength is recommended. Propose a stability protocol. (Refer to ICH Guidelines Q1A and Q1D).

Sponsor clarified that the additional container is for (b) (4).

9. Is PANCRECARB® eligible for an environmental assessment waiver?

FDA Response:

Yes it appears it can be eligible. Refer to the Guideline for Environmental Assessment.

10. Does FDA agree that the data presented in the two clinical studies, and studies reported in the literature supporting the safety and effectiveness of pancreatic

enzymes, are adequate to support the clinical requirements of the NDA? It should be noted that in study 020296, the concentration of the buffer was (b) (4) and in study 97-001-1B, the concentration of the buffer was (b) (4). The latter formulation is currently the manufactured product.

FDA Response:

Clarify which formulations (provide quantitative formulation information) are used for each study you are referring to. A bridging study might be required since your product is not fully characterized.

In general, two adequate and well controlled clinical studies using the formulation to be marketed are required. However, the adequacy of the data for approval is a review issue.

Based on the preliminary review of the limited data provided, we have the following comments:

- **The CF Foundation Consensus Statement defined dosing guidelines and set upper limits of lipase for CF patients. Please clarify the dosing determination in your studies.**
- **Your studies did not involve children under age 8. Pancreatic enzyme is used in infants, toddlers, and pre-school-age children with CF (b) (4). Appropriate supporting data are required for these age groups.**
- **Please clarify whether your primary outcome measure is consistent with a coefficient of fat absorption. If not, you should provide scientific justification for using a different outcome measure.**
- **Please clarify whether subjects ingested a standardized meal during the study.**
- **The drug is intended for life-long therapy. Accordingly, your safety database should include sufficient number of subjects along with sufficient length of exposure to the drug for the intended indication.**

Sponsor will conduct additional clinical trial using the to-be-marketed drug formulation.

11. What is the final acceptable date for submission of the NDA?

FDA Response:

Refer to the Federal Register Notice 69 FR 23410 of April 28, 2004. You can submit your NDA any time prior to April 28, 2007.

12. When will the final guidelines be issued?

FDA Response:

We do not have information regarding the timeline.

13. Will the division accept a paper-based NDA?

FDA Response:

It is not clear what you are referring to. If you are referring to a 505(b)(2) submission, it may be acceptable. If you are referring to the physical attributes of the NDA submission, paper is acceptable, although we highly encourage the submission of electronic NDAs.

14. Is there a user fee exemption for pancreatic enzymes since cystic fibrosis is an orphan indication?

FDA Response:

In order to receive a user fee exemption you need to have obtained orphan status. You should have additional discussions with the Office of Orphan Products Development as requested in letter dated October 21, 2004.

Additional comment to the company:

- **Consider conducting stability studies at refrigerated conditions to minimize loss of potency of the drug product.**

Minutes Preparer: _____
Monika Houstoun, Pharm.D.
Regulatory Project Manager

Chair Concurrence: _____
Ruyi He, M.D.
Medical Team Leader

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

/s/

Monika Houstoun
7/21/05 04:32:13 PM

Ruyi He
7/21/05 05:22:12 PM