

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-175Orig1s000**

**OTHER REVIEW(S)**

**505(b)(2) ASSESSMENT**

<b>Application Information</b>		
NDA # 022175	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Pertzye Established/Proper Name: pancrelipase Dosage Form: Delayed Release Capsules Strengths: MS-8 (Lipase: 8,000 USP units), and MS-16 (Lipase 16,000 USP units)		
Applicant: Digestive Care, Incorporated		
Date of Receipt: October 27, 2008		
PDUFA Goal Date: May 18, 2012		Action Goal Date (if different): May 17, 2012
Proposed Indication(s): Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions.		

**GENERAL INFORMATION**

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?
- YES  NO

*If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*



**INFORMATION PROVIDED VIA RELIANCE  
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Published Literature	<b>Pharmacology/Toxicology:</b>  Nonclinical safety of the excipients (sodium carbonate, NF; sodium bicarbonate, USP; sodium starch glycolate, NF; ursodiol, USP; polyvinyl pyrrolidone, USP; celluloase acetate phthalate, NF; diethyl phthalate, NF; talc, USP) used in Pancrecarb were evaluated based on the information obtained from the published literature such as:
Published Literature	Concise International Chemical Assessment Document 52, Diethyl Phthalate, WHO 2003
Published Literature	Screening Information Dataset (SIDS Initial Assessment Report for SIAM 15, October, 2002)
Published Literature	EPA, 40 CFR180, OPP-301210; FRL-6818-2, RIN 2070-AC18

\*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Clinical:

The Clinical reviewer relies heavily on published literature to approve the Pancreatic Enzyme Products. From a clinical standpoint, per the Guidance, long-term safety and efficacy is based on the large body of information with many different PEPs in the treatment of children with Cystic Fibrosis (CF). CF children grow better, have better nutrition, less morbidity (e.g. infections), and longer lives due to PEP treatment (and other advances). This is felt to have been well established over the years in hundreds-thousands of published papers, and is clearly standard of care. However, literature is not for one PEP specifically (such as Cotazym), but an accumulation of knowledge with the entire PEP experience. Thus, the Guidance states the applicants only have to show short-term safety and efficacy because of the large body of available literature/evidence. Otherwise, these short-term study designs (and acceptance of

just one small study) would not have been acceptable for establishing clinical safety and efficacy.

**RELIANCE ON PUBLISHED LITERATURE**

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES  NO

*If "NO," proceed to question #5.*

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES  NO

*If "NO," proceed to question #5.*

*If "YES", list the listed drug(s) identified by name and answer question #4(c).*

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES  NO



**RELIANCE ON LISTED DRUG(S)**

*Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.*

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES  NO

*If "NO," proceed to question #10.*

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)

*Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A  YES  NO

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".*

*If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES  NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES  NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES  NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

*The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.*

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

**(Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).

**Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES  NO

If "**NO**" to (a) proceed to question #11.  
If "**YES**" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?  
YES  NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?  
YES  NO

If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES  NO

If "**NO**", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?  
YES  NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?  
YES  NO

If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): Creon (pancrelipase), Zenpep (pancrelipase), Pancreaze (pancrelipase), Ultresa (pancrelipase)

**PATENT CERTIFICATION/STATEMENTS**

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): **N/A (no reference listed drug)**

No patents listed  *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES  NO

*If "NO", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s): **N/A (no reference listed drug)**

- 14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the*

*NDA holder/patent owner, proceed to question #15.*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
  
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):  
Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

- (a) Patent number(s):
- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?  
YES  NO   
*If "NO", please contact the applicant and request the signed certification.*

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.  
YES  NO   
*If "NO", please contact the applicant and request the documentation.*

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

**Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES  NO  Patent owner(s) consent(s) to an immediate effective date of approval

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JAGJIT S GREWAL  
05/17/2012

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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NDA #/Product Name: NDA 022175 Pertzye (pancrelipase) Delayed-Release Capsules

PMR/PMC Description: 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.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>
	Other: <u>Supplement Submission Date</u>	<u>06/30/2014</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The low weight pediatric patients are a small subpopulation affected.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

In order to give the proper dose of PEPs to low weight pediatric patients, a formulation needs to be developed which can dose them correctly without using partial doses.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)  
 Animal Efficacy Rule  
 Pediatric Research Equity Act  
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?  
 Assess signals of serious risk related to the use of the drug?  
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The Sponsor agrees to develop a formulation for Pertzye which will allow dosing to the youngest, lowest weight pediatric patients who will be administered 2,000 to 4,000 lipase units per 120 mL of formula or per breast-feeding.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)  
Development of a specific formulation for Pertzye which will allow lipase doses of 2,000 to 4,000 lipase units (per 120 mL of formula or per breast-feeding) to be administered to pediatric patients.
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- 
- Other  
Development of a specific formulation for Pertzye which will allow lipase doses of 2,000 to 4,000 lipase units (per 120 mL of formula or per breast-feeding) to be administered to pediatric patients.
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

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NDA #/Product Name: NDA 022175 Pertzye (pancrelipase) Delayed-Release Capsules

PMR/PMC Description: 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.

PMR/PMC Schedule Milestones: Final Protocol Submission: 05/2013  
Study/Trial Completion: 07/2023  
Final Report Submission: 07/2024  
Other: \_\_\_\_\_ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The safety of PEPS is well established based on ample information available in the medical literature. Fibrosing colonopathy has been reported following treatment with different pancreatic enzyme products. Fibrosing colonopathy is a rare, serious adverse reaction initially described in association with high-dose pancreatic enzyme use, usually over a prolonged period of time and most commonly reported in pediatric patients with cystic fibrosis.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

In the drug class of Pancrelipase, there were cases of fibrosing colonopathy identified. Fibrosing colonopathy is a serious, rare condition that has been described in association with high-dose pancreatic enzyme use.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Ten year observational safety study to evaluate the incidence of a specific serious and severe adverse event (fibrosing colonopathy).

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other  
Ten year observational study to evaluate the incidence of a specific serious and severe adverse event (fibrosing colonopathy).
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
  - Are the objectives clear from the description of the PMR/PMC?
  - Has the applicant adequately justified the choice of schedule milestone dates?
  - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- 

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

## PMR/PMC Development Template

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NDA #/Product Name: NDA 022175 Pertzye (pancrelipase) Delayed-Release Capsules

PMR/PMC Description: 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.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>05/2013</u>
	Study/Trial Completion:	<u>07/2018</u>
	Final Report Submission:	<u>07/2019</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The safety of PEPS is well established based on ample information available in the medical literature; however, since all PEPs contain porcine viruses, there is a theoretical risk of transmission of selected porcine viruses to patients taking Pertzye.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Since all PEPs contain porcine viruses, there is a theoretical risk of transmission of selected porcine viruses to patients taking Pertzye.

There is a theoretical risk of transmission of selected porcine viruses to patients taking Pertzye, thus porcine viruses can potentially infect patients taking Pertzye. Infection with these viruses can potentially lead to illness.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An observational study to estimate the prevalence of antibody seropositivity to selected porcine viruses in patients taking Pertzeye compared with an appropriate control group.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other  
Observational study to estimate the prevalence of antibody seropositivity to selected porcine viruses in patients taking Pertzye.
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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NDA #/Product Name: NDA 022175 Pertzze (pancrelipase) Delayed-Release Capsules

PMR/PMC Description: Provide an assessment of the viral inactivation capability of the cleaning agents currently used in the facility.

PMR/PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY  
Study/Trial Completion: MM/DD/YYYY  
Final Report Submission: 09/01/2012  
Other: \_\_\_\_\_ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need  
 Life-threatening condition  
 Long-term data needed  
 Only feasible to conduct post-approval  
 Prior clinical experience indicates safety  
 Small subpopulation affected  
 Theoretical concern  
 Other

The sponsor needs to evaluate the ability of the cleaning agents used in the facility to inactivate viral agents. This assessment will take time to design and execute. Since the sponsor has assays in place that will be used to monitor for the presence of viral agents, the absence of a formal evaluation of the inactivation capability of the cleaning agents does not preclude approval of the application. The company currently uses detergents, (b) (4) to clean equipment. These agents are known to inactivate viral and microbial agents, and their use thus provide some assurance that viral agents will be inactivated.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

During the inspection of the drug substance manufacturing facility, the inspectors noted that the manufacturer cleaning procedures were not robust, which resulted in a citation. The manufacturer committed to improve the cleaning procedures, but did not provide an evaluation of the viruses-inactivation capability of the cleaning agents. Although the cleaning agents used by the sponsor have the potential to inactivate viral and microbial agents, a formal assessment is necessary to address this issue.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The sponsor should assess the capability of the cleaning agents to inactivate viruses. This assessment can be conducted as a laboratory study or as a formal risk assessment that takes into consideration the chemical characteristic of the agent and the biology of the viral agents.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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NDA #/Product Name: NDA 022175 Pertzye (pancrelipase) Delayed-Release Capsules

PMR/PMC Description: Develop and validate an infectivity assay for PCV1 (Porcine Circovirus 1).

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PMR/PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY  
Study/Trial Completion: MM/DD/YYYY  
Final Report Submission: 03/01/2013  
Other: \_\_\_\_\_ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The (b) (4) drug substance and all PEP products have been shown to contain PCV1 genome equivalents indicative of the presence of this virus. It is not clear how genome equivalents translate to infectious particles but live virus presents a theoretical risk to patient safety. Although the virus has not been reported to cause human disease (and is probably present in porcine products that are ingested by humans), it is well documented that in extremely rare cases viruses can change species tropism leading to an infectious disease. This risk can be further mitigated by ensuring drug product has minimal live virus present in each dose consistent with manufacturing process history and our understanding of the virus's biology. DTP has established a policy that a PCV 1 infectious assay should be developed and used for lot release for all PEP products as recommended in the advisory committee meeting on viral issues for PEP products. The risk is low and these assays take time to develop so we believe it is appropriate to address this issue as a PMC

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

ICH Q5A and the 2006 FDA PEP guidance have indicated that the pancrelipase manufacturing process should be robust to ensure removal of viral adventitious agents. PCV1 is a non enveloped virus that is likely to be present in these products yet the PEP manufacturing process demonstrates no capability to inactivate non enveloped viruses. Therefore (b) (4) should monitor for the virus and reject lots that contain unusual levels of the infectious agent and present a risk to patient safety.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

<p>(b) (4) should develop a cell-based assay to monitor for infectious PCV1</p>
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Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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NDA #/Product Name: NDA 022175 Pertzze (pancrelipase) Delayed-Release Capsules

PMR/PMC Description: Establish lot release specifications for PPV (Porcine Parvovirus) and PCV2 (Porcine Circovirus 2) for the drug substance.

PMR/PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY  
Study/Trial Completion: MM/DD/YYYY  
Final Report Submission: 03/01/2013  
Other: \_\_\_\_\_ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need  
 Life-threatening condition  
 Long-term data needed  
 Only feasible to conduct post-approval  
 Prior clinical experience indicates safety  
 Small subpopulation affected  
 Theoretical concern  
 Other

The (b) (4) drug substance and all PEP products have been shown to contain PPV and PCV2 virus. In order to establish appropriate and meaningful specifications, the sponsor will need to manufacture several lots of drug substance to fully understand the capability of the process to reduce the load of these two viruses. These viruses are not known to infect humans but there is a theoretical risk that mutations or genetic recombination events could change species specificity so control of these viruses is warranted.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

ICH Q5A and the 2006 FDA PEP guidance have indicated that the pancrelipase manufacturing process should be robust to ensure removal of viral adventitious agents. PCV2 and PPV are non enveloped virus that are present in these products. PEP manufacturing process demonstrates little or no capability to inactivate non enveloped viruses. Therefore (b) (4) should monitor for the viruses and reject lots that do not meet specifications and contain unusual levels of the infectious agent and present a risk to patient safety. These virus are not associate with human infection and are likely present in porcine meat products consumed by humans.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The sponsor should implement assays to monitor for infectious PPV and PCV2
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**Required**

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

Other

---

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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NDA #/Product Name: NDA 022175 Pertzye (pancrelipase) Delayed-Release Capsules

PMR/PMC Description: Perform additional monitoring of viral load entering the manufacturing process. The control program will include the selection of human pathogenic viruses for monitoring by qPCR. An appropriate control strategy should be proposed.

PMR/PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY  
Study/Trial Completion: MM/DD/YYYY  
Final Report Submission: 05/15/2013  
Other: \_\_\_\_\_ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The current PCR assays sensitivity is sub optimal since the limit of detection is only (b) (4) genome equivalents per gram of drug substance. This level is anticipated to be beyond the capacity of the manufacturing process to inactivate some viruses. However, it is not clear what viral loads are in the starting material. While this is an important issue, availability of these products is critical and the risk to product quality has already been greatly reduced as compared to current marketed product. Again the risk is theoretical in that no infectious diseases are known to have been transmitted by the unapproved PEPs.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

ICH Q5A and the 2006 FDA PEP guidance have indicated that the pancrelipase manufacturing process should be robust to ensure removal of viral adventitious agents. The (b) (4) process demonstrates little capability to inactivate non enveloped viruses. Therefore, the sponsor should monitor for the virus loads entering the process and in the drug substance with sensitive assays. Lots that contain the infectious agents that cause disease in humans should be rejected.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The sponsor should select viruses that have the potential to infect human and develop appropriate quantitative, PCR based assays to assess the viral load in incoming materials.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

Other

---

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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NDA #/Product Name: NDA 022175 Pertzze (pancrelipase) Delayed-Release Capsules

PMR/PMC Description: 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 will be submitted to the Agency.

PMR/PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY  
Study/Trial Completion: MM/DD/YYYY  
Final Report Submission: 04/15/2013  
Other: \_\_\_\_\_ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need  
 Life-threatening condition  
 Long-term data needed  
 Only feasible to conduct post-approval  
 Prior clinical experience indicates safety  
 Small subpopulation affected  
 Theoretical concern  
 Other

The current PCR assays sensitivity is sub optimal since the limit of detection is only (b) (4) genome equivalents per gram of drug substance. The starting material for one lot is (b) (4). Therefore, with the current assays, the sensitivity would be (b) (4) genome equivalent per lot. While this is an important issue, availability of these products is critical and the risk to product quality has already been greatly reduced as compared to current marketed product. The risk is theoretical in that no infectious diseases are known to have been transmitted by the unapproved PEPs.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

ICH Q5A and the 2006 FDA PEP guidance have indicated that the pancrelipase manufacturing process should be robust to ensure removal of viral adventitious agents. The (b) (4) process demonstrates no capability to inactivate non enveloped viruses. Therefore, (b) (4) should monitor for the virus with sensitive assays and reject lots that contain the infectious agents. All of the virus in this PMC have the potential to cause human infections. This was a PMC for the Creon, Zenpep, and Pancrease products.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The sponsor should improve the assays currently in use to increase sensitivity and propose new acceptance criteria based on the improved assays.

**Required**

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
  - Are the objectives clear from the description of the PMR/PMC?
  - Has the applicant adequately justified the choice of schedule milestone dates?
  - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- 

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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NDA #/Product Name: NDA 022175 Pertzye (pancrelipase) Delayed-Release Capsules

PMR/PMC Description: Assess the risk to product quality associated with hokovirus, and to submit a control strategy for mitigating the risk to product quality.

PMR/PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY  
Study/Trial Completion: MM/DD/YYYY  
Final Report Submission: 06/01/2012  
Other: \_\_\_\_\_ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need  
 Life-threatening condition  
 Long-term data needed  
 Only feasible to conduct post-approval  
 Prior clinical experience indicates safety  
 Small subpopulation affected  
 Theoretical concern  
 Other

Hokovirus has only recently been identified in porcine material in south east Asia but has never been detected in the pig population on the US or Europe. The virus can infect humans, but has never be detected in humans in the US or Europe. Since the source material for pancrelipase is <sup>(b)</sup>(4), the risk to patients is low. However, the sponsor should work proactively and implement a surveillance program that routinely evaluates the risk from this virus in case it spreads to the <sup>(b)</sup>(4) pig population.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

ICH Q5A and the 2006 FDA PEP guidance have indicated that the pancrelipase manufacturing process should be robust to ensure removal of viral adventitious agents. Hokovirus has only recently been identified in swine and therefore little information is available. The sponsor’s surveillance program should include continual monitoring of the literature to ensure that quality systems could be updated to control for this viurus (e.g. herd surveillance programs) and other emerging new viral agents that infect humans.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The sponsor should implement a surveillance program to monitor for the emergence of hokovirus in the pig herds.
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Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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NDA #/Product Name: NDA 022175 Pertzze (pancrelipase) Delayed-Release Capsules

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

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>03/15/2013</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need  
 Life-threatening condition  
 Long-term data needed  
 Only feasible to conduct post-approval  
 Prior clinical experience indicates safety  
 Small subpopulation affected  
 Theoretical concern  
 Other

Ebola virus has only recently been identified in porcine material in south east Asia but has never been detected in the pig population on the US or Europe. The virus can infect humans, but has never been detected in humans in the US or Europe. Since the source material for pancrelipase is (b) (4), the risk to patients is low. Additionally, Ebola is an enveloped virus and thus can be inactivated by the (b) (4) step in the process, further reducing the risk to patients. Regardless, the sponsor should implement a surveillance program that routinely evaluates the risk from this virus to emerge in the (b) (4) swine herds.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

ICH Q5A and the 2006 FDA PEP guidance have indicated that the pancrelipase manufacturing process should be robust to ensure removal of viral adventitious agents. The process does have the capability to inactivate enveloped viruses and thus should inactivate the Ebola virus. Ebola virus has only recently been identified in swine and therefore little information is available. The sponsor’s surveillance program should include continual monitoring of the literature to ensure that quality systems could be updated to control for this virus (e.g. herd surveillance programs) and other emerging new viral agents that infect humans.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The sponsor should implement a surveillance program to monitor for the emergence of Ebola virus in pig herds.
---

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

Other

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5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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MF #/Product Name: NDA 022175 Pertzze (pancrelipase) Delayed-Release Capsules

PMR/PMC Description: 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.

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PMR/PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY  
Study/Trial Completion: MM/DD/YYYY  
Final Report Submission: 06/01/2012  
Other: \_\_\_\_\_ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

(b) (4) drums are used for drug substance intermediate storage, for (b) (4). Although (b) (4) is a relatively inert material, metal ions could potentially leak into the drug substance. Metal ions have the potential to chemically react with the proteins in the pancrelipase drug substance. Therefore, although the risk to product quality is low, a study to evaluate the potential of metal ions to leak from the (b) (4) containers is warranted.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of this study is to determine the extent of metal ions leaching into pancrelipase drug substance and to perform a risk assessment and if necessary, develop a control strategy.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The type of study that is warranted is inductively coupled plasma mass spectrometry (ICP-MS) as a sensitive way to measure metal ions in pancrelipase drug substance under leachable conditions.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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MF #/Product Name: NDA 022175 Pertzye (pancrelipase) Delayed-Release Capsules  
PMR/PMC Description: Revise release specifications after 30 lots of 1206 and 1208 drug substance have been manufactured.

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PMR/PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY  
Study/Trial Completion: MM/DD/YYYY  
Final Report Submission: 05/15/2013  
Other: \_\_\_\_\_ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The current release specifications for drug substance are adequate to ensure product quality but more robust programs should be developed to provide a better assurance of product quality. While the lots produced so far have shown acceptable results that are in-line with the manufacturing history and clinical experience, there is a risk that maintaining the current acceptance criteria could potentially result in lots that are within specification but out of trend with lots used in the clinical trials. To established process capability and reduce the risk to product quality, a larger number of product lots are necessary which could not be accomplished during the review cycle.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Assays used for release testing of drug substance are adequate for approval. Proposed acceptance criteria for drug substance release specifications are wide and should be based on manufacturing history and clinical experience, once the sponsor gains sufficient information through manufacturing of multiple lots.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

<p>(b) (4) should re-evaluate the release specifications for drug substance and tighten acceptance criteria based on results of lots manufactured with the clinical and commercial processes.</p>
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Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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NDA #/Product Name: NDA 022175 Pertzze (pancrelipase) Delayed-Release Capsules

PMR/PMC Description: Revise release and stability specifications after 30 lots of drug product have been manufactured.

PMR/PMC Schedule Milestones: Final Protocol Submission: \_\_\_\_\_

Study/Trial Completion: MM/DD/YYYY

Final Report Submission: December 2015

Other: \_\_\_\_\_ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The current release and stability specifications for drug product are adequate to ensure product quality and stability but more robust programs should be developed to provide a better assurance of product quality. While the lots produced so far have shown acceptable results that are in-line with the manufacturing history and clinical experience, there is a risk that maintaining the current acceptance criteria could potentially result in lots that are within specification but out of trend with lots used in the clinical trials. To establish process capability and reduce the risk to product quality, a larger number of product lots are necessary which could not be accomplished during the review cycle.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Assays used for release and stability testing of drug product are adequate for approval. Proposed acceptance criteria for drug product release and stability specifications are wide and should be based on manufacturing history and clinical experience, once the sponsor gains sufficient information through manufacturing of multiple lots.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

DCI should re-evaluate the release and stability specifications for drug product and tighten acceptance criteria based on results of lots manufactured with the clinical and commercial processes.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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NDA #/Product Name: NDA 022175 Pertzze (pancrelipase) Delayed-Release Capsules

PMR/PMC Description: 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 current manufacturing experience.

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PMR/PMC Schedule Milestones: Final Protocol Submission: July 2012  
Study/Trial Completion: MM/DD/YYYY  
Final Report Submission: MM/DD/YYYY  
Other: \_\_\_\_\_ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The stability data provided supports the drug substance and drug product dating periods and current cumulative data for drug product lots that will be marketed but does not include drug product produced with drug substance at the end of its expiry period. The concern is only for material that in the future could exceed current cumulative storage times for drug substance and drug product. Therefore to control this risk the applicant should propose a protocol that places on stability lots of drug product manufactured with drug substance aged past what the manufacturer experience has been.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The sponsor has used drug substance of various ages and established a stability profile and expiry for the drug product. However, the sponsor may receive drug substance close to its own expiry date and there is little information on what the cumulative stability of the drug substance might be. For protein products extrapolation of existing stability data is not appropriate and therefore real time, real condition studies should be performed. The goal of this protocol is to confirm that product manufactured with drug substance aged past what the manufacturer experience has been, maintains an adequate stability profile throughout its shelf life.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A stability study will be required each time the manufacturer exceeds the cumulative storage time of the drug substance/drug product. Data supporting the cumulative time will be submitted in the annual report as is typical for these types of studies using an agreed to protocol.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

---

NDA #/Product Name: NDA 022175 Pertzye (pancrelipase) Delayed-Release Capsules

PMR/PMC Description: Establish an expiration date for the RP-HPLC column.

PMR/PMC Schedule Milestones: Final Protocol Submission: \_\_\_\_\_  
Study/Trial Completion: MM/DD/YYYY  
Final Report Submission: July 2015  
Other: \_\_\_\_\_ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The system suitability component of this assay test method ensures that RP-HPLC column is performing adequately for routine lot release testing.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The sponsor will need time to perform the assay and determine when columns are no longer performing appropriate to establish a shelf life.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The RP-HPLC assay is routinely performed for lot release and stability testing of the drug product. The column is cleaned and reused routinely. The sponsor will determine an expiration date for the column as defined at the time point that the suitability control fails. The sponsor will need to evaluate multiple columns to determine an accurate expiration date.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

---

NDA #/Product Name: NDA 022175 Pertzze (pancrelipase) Delayed-Release Capsules

PMR/PMC Description: Establish a primary reference standard against which future reference standards will be qualified.

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PMR/PMC Schedule Milestones: Final Protocol Submission: \_\_\_\_\_  
Study/Trial Completion: MM/DD/YYYY  
Final Report Submission: December 2012  
Other: \_\_\_\_\_ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The current USP reference standard is acceptable. However, ICH Q6B recommends establishing primary reference material against which future standards are qualified. This helps to minimize drifts in product attributes overtime.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The sponsor will need time to establish a primary reference standard and will therefore address this issue after approval of the application.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The sponsor will need to evaluate current drug substance lots or to manufacture a new lot to select a reference standard. The reference standard should have product attributes that are highly similar to the clinical lot. The reference standard will need to be stored under conditions that it is most stable. Thus, time will be required to develop appropriate procedures.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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NDA #/Product Name: NDA 022175 Pertzye (pancrelipase) Delayed-Release Capsules

PMR/PMC Description: Perform *in vitro* studies to determine the feasibility of administering the contents of Pertzye (pancrelipase) Delayed-Release Capsules through a gastrostomy tube.

PMR/PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY  
Study/Trial Completion: MM/DD/YYYY  
Final Report Submission: 06/2013  
Other: \_\_\_\_\_ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Patients that require PEPs to be administered via gastrostomy tubes are a small subpopulation affected.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

PEPs, including Pertzye, are not approved for administration via gastrostomy tubes. However, a small number of patients may require PEPs to be given through this route. In order to evaluate the feasibility of administering Pertzye via gastrostomy tubes, the Applicant has committed to conducting *in vitro* testing.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The Applicant will conduct *in vitro* testing to evaluate the feasibility of administering Pertzye via gastrostomy tubes.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

Other

The Applicant will conduct *in vitro* testing to evaluate the feasibility of administering Pertzye via gastrostomy tubes.

---

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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NDA #/Product Name: NDA 022175 Pertzye (pancrelipase) Delayed-Release Capsules

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PMR/PMC Description: 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.
- 

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>05/2013</u>
	Other: _____	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

In the previous cycle, the Applicant had been suggested to consider conducting dissolution testing using the USP dissolution method (i.e., in the acid stage for one hour and then transfer the contents to the buffer stage). The Applicant's proposed method and acceptance criterion are acceptable on an interim basis, and thus dissolution testing does not preclude approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

For the setting of the final dissolution method and acceptance criterion, the Applicant should provide additional dissolution profile data (individual, mean, plots, n= 12) for both MS-8 and MS-16 strengths of the proposed Pertzye DR capsules.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The Applicant is to conduct dissolution testing using the USP Method <711>, to incubate the product in the acid stage for 1 hour and then transfer the contents to the buffer stage. A sample of the buffer solution will be collected at specified times. The Applicant is to proceed as directed for assay for lipase activity. Additional dissolution profile data will be collected from at least 3 production batches of each product strength. The dissolution data from these production batches will be used to set the buffer stage dissolution acceptance criterion for the product.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JAGJIT S GREWAL  
05/16/2012

ANIL K RAJPAL  
05/16/2012



Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research

Office of Biotechnology Products  
Federal Research Center  
Silver Spring, MD  
Tel. 301-796-4242

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## Memorandum

### PROJECT MANAGER'S REVIEW

Application Number: NDA 22-175

Name of Drug: PERTZYE<sup>®</sup> (pancrelipase) Delayed-Release Capsules

Sponsor: Digestive Care, Inc.

Material Reviewed: Carton and Container Labels

Receipt Date: February 4, 2009, November 18, 2011, February 17, 2012,  
March 9, 2012, March 29, 2012

### EXECUTIVE SUMMARY

The carton and container labels for PERTZYE<sup>®</sup> (pancrelipase) Delayed-Release Capsules were reviewed and found to comply with the following regulations: 21 CFR 201.1 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57 and 21 CFR 200.100. USPC Official 12/1/11-4/30/12, USP 34/NF 29. Labeling deficiencies were identified and mitigated. Please see comments in the conclusions section. The proposed labels submitted March 29, 2012 (including 8,000 and 16,000 Lipase units) in 100 and 250 count configurations are acceptable.

#### Background:

PERTZYE<sup>®</sup> (pancrelipase) Delayed-Release Capsules is a New Drug Application (NDA) indicated for patients with exocrine pancreatic insufficiency associated with cystic fibrosis, (b) (4) or other conditions. PERTZYE is a pancreatic enzyme product (PEP) consisting of porcine-derived lipase, protease, and amylase.

#### Labels Reviewed:

PERTZYE<sup>®</sup> (Pancrelipase) Delayed Release Capsules Container and Carton Labels  
10 pages of Draft Carton and Container Labels have been Withheld in Full as b4 (CCI/TS)  
immediately following this page

## I. Container

### A. Bottle Label

1. 21 CFR 201.1 Drugs; name and place of business of manufacturer, packer or distributor-  
“Manufactured in the USA by: DIGESTIVE CARE, INC.  
1120 Win Drive  
Bethlehem, PA 18017”
2. 21 CFR 201.2 Drugs and devices; National Drug Code numbers-  
The National Drug Code (NDC) number is located above the proprietary name at the top of the label. It is noted as NDC XXXXX -XXX-XX. The NDC number conforms to 21 CFR 207.35 as a 3-2 Product-Package Code configuration. This conforms to the regulation.
3. 21 CFR 201.5 Drugs; adequate directions for use-Directions for use do not appear on the label; however “See package insert for dosing information.” appears on the side panel. This conforms to the regulation.
4. 21 CFR 201.6 Drugs; misleading statements- The proprietary name, PERTZYE<sup>®</sup> and the established name, (pancrelipase) Delayed Release Capsules appears on the label. This conforms to the regulation.
5. 21 CFR 201.10 Drugs; statement of ingredients- The established name, pancrelipase is used in type at least half as large as the most prominent presentation of the proprietary name, PERTZYE<sup>®</sup>. This conforms to the regulation.

6. 21 CFR 201.15 Drugs; prominence of required label statements- All required statements (“Rx Only” and other pertinent statements). This conforms to the regulation.
7. 21 CFR 201.17 Drugs: location of expiration date-The expiration date appears under the lot identification number on the side of the label. This conforms to the regulation.
8. 21 CFR 201.25 Bar code label requirements – The bar code is located on the side of the label with sufficient white space surrounding to ensure for proper scanning.
9. 21 CFR 201.50 Statement of identity- The ingredients, Lipase, Amylase and Protease are listed with corresponding units per capsule per 21 CFR 201.10. This conforms to the regulation.
10. 21 CFR 201.51 Declaration of net quantity of contents – The label states the net quantity of contents in terms of numerical count of capsules at the top of the label. This conforms to the regulation.
11. 21 CFR 201.55 Statement of dosage- The label states “Dosage and Administration: Dose by lipase units. See package insert for dosing information.” This conforms to the regulation and conforms to the United States Pharmacopeia, 12/1/11-4/30/12, USP 34/NF 29, Monograph-Pancrelipase.
12. 21 CFR 201.100 Prescription drugs for human use- The label bears statements “Rx Only”, an identifying lot number, storage conditions, and a reference to the package insert.”
13. 21 CFR 208.24 Distribution and dispensing of a Medication guide- If a Medication Guide is required under part 208 of chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label. A medication guide statement appears on the label, “Pharmacist: Dispense the accompanying Medication Guide to each patient”. This conforms to the regulation.

13 pages of Draft Carton and Container Labels have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

**II. Carton**

1. 21 CFR 201.1 Drugs; name and place of business of manufacturer, packer, or distributor- The label states:  
“Manufactured in the USA by: Digestive Care, Inc.  
Digestive Care, Inc.  
Bethlehem, PA 18017”

2. 21 CFR 201.2 Drugs and devices; National Drug Code numbers- The National Drug Code (NDC) number is located above the proprietary name at the top of the label. It is noted as NDC XXXXX-XXX-XX. The NDC number conforms to 21 CFR 207.35 as a 3-2 Product-Package Code configuration. This conforms to the regulation.
3. 21 CFR 201.5 Drugs; adequate directions for use-On the side of the label “Dosage and Administration: Dose by lipase units. See package insert for dosing information.” appears. This conforms to the regulation.
4. 21 CFR 201.6 Drugs; misleading statements - The proprietary name, Pertzye™ appears with the established name, pancrelipase on the carton. This conforms to the regulation.
5. 21 CFR 201.10 Drugs; statement of ingredients- The established name, pancrelipase is used in type at least half as large as the most prominent presentation of the proprietary name, Pertzye™. This conforms to the regulation.
6. 21 CFR 201.15 Drugs; prominence of required label statements- All required statements (“Rx Only”, “Protect from moisture” and other pertinent statements appear on the label. This conforms to the regulation.
7. 21 CFR 201.17 Drugs; location of expiration date - The expiration date appears below the lot number on the carton. This conforms to the regulation.
8. 21 CFR 201.25 Bar code label requirements - The bar code is located at the bottom of a side panel of the carton with sufficient white space surrounding to ensure for proper scanning. This conforms to the regulation.
9. 21 CFR 201.50 Statement of identity - The ingredients, Lipase, Amylase and Protease are listed with corresponding units per capsule per 21 CFR 201.10. This conforms to the regulation.
10. 21 CFR 201.51 Declaration of net quantity of contents - The label states the net quantity of contents in terms of numerical count in units at the top of the carton. Each strength is available in (b) (4) 100 count, and a 250 count. This conforms to the regulation.

11. 21 CFR 201.55 Statement of dosage - The label states “Dosage and Administration: Dose by lipase units. See package insert for dosing information.” This conforms to the regulation.
12. 21 CFR 201.100 Prescription drugs for human use - The label bears statements, “Rx Only”, an identifying lot number, storage conditions, and a reference to the package insert. This conforms to the regulation.
13. 21 CFR 208.24 Distribution and dispensing of a Medication guide- If a Medication Guide is required under part 208 of chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label. This conforms to the regulation. The following statement appears on the carton label, “Pharmacist: Dispense the accompanying Mediation Guide to each patient”.

### III. Conclusions

- A. The proposed carton and container labeling submitted March 9, 2012 are acceptable. (b) (4)  
The approved labels are for the 8,000 and 16,000 Lipase unit container and carton labels (b) (4)  
The product will be manufactured in 100 and 250 count configurations.

Note: The initial labels submitted on February 4, 2009 (below) were significantly revised and included the following designations:

(b) (4)  
MS-8 (8,000) Lipase Units -100ct and 250ct  
S-16 (16,000) Lipase Units -100ct and 250ct

#### Submitted February 4, 2009

(b) (4)



(b) (4)

Carton MS-8, 100 capsules



(b) (4)

Carton MS-8, 250 capsules



(b) (4)

Carton MS-16, 100 capsules



Carton MS-16, 250 capsules



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Kimberly Rains, Pharm.D  
Regulatory Project Manager  
CDER/OPS/OBS

Comment/Concurrence:

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Howard Anderson, Ph.D.  
Product Reviewer  
Division of Therapeutic Proteins  
CDER/OPS/OBP/

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Emanuela Lacana, Ph.D.  
Team Leader  
Division of Therapeutic Proteins  
CDER/OPS/OBP

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/s/  
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KIMBERLY M RAINS  
04/17/2012

HOWARD A ANDERSON  
04/17/2012

EMANUELA LACANA  
04/17/2012

## SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: No Format Deficiencies

<b>Product Title</b>	<b>PERTZYE (pancrelipase) delayed-release capsules, for oral use</b>
Applicant	Digestive Care, Inc.
Application/Supplement Number	NDA 022175
Type of Application	Class 2 Resubmission
Indication(s)	For the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions
Established Pharmacologic Class <sup>1</sup>	Combination of porcine-derived lipases, proteases, and amylases
Office/Division	ODE III/DGIEP
Division Project Manager	Jagjit Grewal
Receipt Date	November 18, 2011
PDUFA Goal Date	May 18, 2012
SEALD Review Date	April 16, 2012
SEALD Labeling Reviewer	Jeanne M. Delasko
SEALD Division Director	Laurie Burke

<sup>1</sup> The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, final agreed-upon prescribing information (PI) for critical format elements reveals **NO outstanding labeling format issues** and the SEALD Director has **NO OBJECTION** to the approval of this PI at this time.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements for Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **YES**: The PI **meets** the requirement for this item (**not a deficiency**).
- **NO**: The PI **does not meet** the requirement for this item (**deficiency**).
- **N/A** (not applicable): This item does not apply to the specific PI under review.

# Selected Requirements of Prescribing Information (SRPI)

## Highlights (HL)

### GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

**Comment:**

- YES** 2. Excluding the length of the Boxed Warnings in the HL, the length of the HL is less than or equal to one-half page unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

**Instructions to complete this item:** If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

**a) For the Filing Period (RPM review)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

**b) End-of Cycle Period (SEALD review)**

Based on information received from the RPM, the SEALD reviewer documents that a waiver has been previously granted or will be granted by the review division in the approval letter.

**Comment:**

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

**Comment:**

- YES** 4. White space must be present before each major heading in HL.

**Comment:**

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

**Comment:**

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required
• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a Boxed Warning is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required

## Selected Requirements of Prescribing Information (SRPI) Revised

• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state “None.”)
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

**Comment:**

- YES** 7. A horizontal line must separate HL and Table of Contents (TOC).

**Comment:**

### HIGHLIGHTS DETAILS

#### Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

**Comment:**

#### Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

**Comment:**

#### Product Title

- YES** 10. Product title in HL must be **bolded**.

**Comment:**

#### Initial U.S. Approval

- YES** 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

**Comment:**

#### Boxed Warning

- N/A** 12. All text must be **bolded**.

**Comment:**

- N/A** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

**Comment:**

## Selected Requirements of Prescribing Information (SRPI) Revised

- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

**Comment:**

- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

**Comment:**

- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

**Comment:**

### Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

**Comment:**

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

**Comment:**

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

**Comment:**

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

**Comment:**

### Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

**Comment:**

### Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

**Comment:**

### Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

**Comment:**

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

## Selected Requirements of Prescribing Information (SRPI) Revised

### Comment:

#### Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

### Comment:

#### Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

### Comment:

#### Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

### Comment:

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## Contents: Table of Contents (TOC)

#### GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

### Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

### Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

### Comment:

- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

### Comment:

## Selected Requirements of Prescribing Information (SRPI) Revised

- YES** 32. All section headings must be **bolded** and in UPPER CASE.  
Comment:
- YES** 33. All subsection headings must be indented, not bolded, and in title case.  
Comment:
- YES** 34. When a section or subsection is omitted, the numbering does not change.  
Comment:
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”  
Comment:

### Full Prescribing Information (FPI)

#### GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.  
Comment:
- YES** 37. All section and subsection headings and numbers must be **bolded**.  
Comment:
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

<b>Boxed Warning</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>
<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>

## Selected Requirements of Prescribing Information (SRPI) Revised

12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

**Comment:**

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

**Comment:**

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

**Comment:**

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

**Comment:**

### FULL PRESCRIBING INFORMATION DETAILS

#### Boxed Warning

- N/A** 42. All text is **bolded**.

**Comment:**

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

**Comment:**

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

**Comment:**

#### Contraindications

- YES** 45. If no Contraindications are known, this section must state “None”.

**Comment:**

#### Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

## Selected Requirements of Prescribing Information (SRPI) Revised

*“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”*

### Comment:

- YES** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”*

### Comment:

#### **Patient Counseling Information**

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
  - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
  - “See FDA-approved patient labeling (Patient Information)”
  - “See FDA-approved patient labeling (Instructions for Use)”
  - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

### Comment:

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/s/  
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JEANNE M DELASKO  
04/16/2012

LAURIE B BURKE  
04/17/2012

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion  
Division of Professional Promotion  
Division of Direct-to-Consumer Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** April 12, 2012

**To:** Jagjit Grewal, Senior Regulatory Project Manager  
Division of Gastroenterology and Inborn Errors Products (DGIEP)

**From:** Kathleen Klemm, Regulatory Review Officer  
Division of Professional Promotion (DPP)  
Office of Prescription Drug Promotion (OPDP)

Twyla Thompson, Regulatory Review Officer  
Division of Direct-to-Consumer Promotion (DDTCP)  
OPDP

**CC:** Lisa Hubbard, Professional Group Leader, DDP/OPDP  
Shefali Doshi, Direct-To-Consumer Group Leader, DDTCP/OPDP

**Subject:** NDA 022175  
PERTZYE (pancrelipase) delayed-release capsules, for oral use [Pertzye]  
OPDP Labeling Consult Response

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In response to DGIEP's February 13, 2012, consult request, OPDP has reviewed the draft package insert (PI), carton/container labeling, and Medication Guide for Pertzye and offers the following comments.

OPDP's comments on the PI are based on version 15 of the proposed draft marked-up labeling titled, Package Insert Label.doc, accessed via the e-Room (last modified April 4, 2012 at 5:04 pm). OPDP used the Division of Medical Policy Programs' tracked changes version of the Medication Guide finalized on April 9, 2012 as the base document for review. OPDP's comments on the PI and Medication Guide are provided directly on the document attached below. Please also see below for OPDP's comments on the carton/container labeling.

If you have any questions regarding the PI or carton/container labeling, please contact Kathleen Klemm at 301.796.3946 or [Kathleen.Klemm@fda.hhs.gov](mailto:Kathleen.Klemm@fda.hhs.gov). If you have any questions regarding the Medication Guide, please contact Twyla Thompson at 301.796.4294 or [Twyla.Thompson@fda.hhs.gov](mailto:Twyla.Thompson@fda.hhs.gov).

## Carton/Container Labeling

OPDP has reviewed the following materials, accessed via the EDR (available at \\cdsesub4\NONECTD\NDA022175\4970568):

- [REDACTED] (b) (4)
- 8000-bottle-100capsules.pdf
- 8000-bottle-250capsules.pdf
- [REDACTED] (b) (4)
- 16000-bottle-100capsules.pdf
- 16000-bottle-250capsules.pdf
- [REDACTED] (b) (4)
- 8000-carton-100capsules.pdf
- 8000-carton-250capsules.pdf
- [REDACTED] (b) (4)
- 16000-carton-100capsules.pdf
- 16000-carton-250capsules.pdf

OPDP has no comments on these proposed materials.

17 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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TWYLA N THOMPSON  
04/12/2012

KATHLEEN KLEMM  
04/12/2012

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy Initiatives  
Division of Medical Policy Programs**

**PATIENT LABELING REVIEW**

Date: April 9, 2012

To: Donna Griebel, MD, Director  
**Division of Gastrointestinal and Inborn Errors Products (DGIEP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**  
Sharon R. Mills, BSN, RN, CCRP  
Senior Patient Labeling Reviewer  
**Division of Medical Policy Programs**

From: Barbara Fuller, RN, MSN, CWOCN  
Team Leader, Patient Labeling Team  
**Division of Medical Policy Programs**

Subject: DMPP Review of Patient Labeling (Medication Guide)

Drug Name (established name): PERTZYE (pancrelipase)

Dosage Form and Route: delayed-release capsules

Application Type/Number: NDA 22-175

Applicant: Digestive Care, Inc.

## 1 INTRODUCTION

This review is written in response to a request by the Division of Gastroenterology and Inborn Error Products (DGIEP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Medication Guide (MG) for PERTZYE (pancrelipase) delayed-release capsules.

The Applicant submitted a Complete Response on November 18, 2011, in response to a Complete Response (CR) letter issued by the Agency on January 27, 2011 for original New Drug Application (NDA) 22-175 for PERTZYE (pancrelipase) delayed-release capsules. The proposed indication for PERTZYE (pancrelipase) delayed-release capsules is for the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions.

## 2 MATERIAL REVIEWED

- Draft PERTZYE (pancrelipase) delayed-release capsules Medication Guide (MG) received on November 18, 2011, revised by the Review Division throughout the current review cycle, and provided to DMPP on March 29, 2012.
- Draft PERTZYE (pancrelipase) delayed-release capsules Prescribing Information (PI) received on November 18, 2011, revised by the Review Division throughout the current review cycle, and provided to DMPP on March 29, 2012.
- Approved ULTRESA (pancrelipase) delayed-release capsules comparator labeling dated March 1, 2012.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the MG, the target reading level is at or below an 8<sup>th</sup> grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the prescribing information (PI)
- removed unnecessary or redundant information

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

#### **4 CONCLUSIONS**

The MG is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated versions of the MG are appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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BARBARA A FULLER

04/09/2012

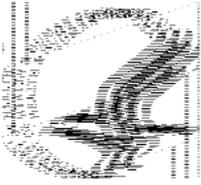
DMPP review of pancrelipase (PERTZYE) NDA 22175 MG

SHARON R MILLS

04/09/2012

LASHAWN M GRIFFITHS

04/09/2012



**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

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Food and Drug Administration  
Office of New Drugs - Immediate Office  
Pediatric and Maternal Health Staff  
Silver Spring, MD 20993  
Telephone 301-796-2200  
FAX 301-796-9744

**M E M O R A N D U M**

**Date:** February 27, 2012

**From:** Elizabeth L. Durmowicz, MD, Medical Officer

**Through:** Hari Cheryl Sachs, MD, Team Leader  
Lisa Mathis, MD, OND Associate Director  
Pediatric and Maternal Health Staff, Office of New Drugs

**To:** Marjorie Dannis, MD, Clinical Reviewer  
Anil Rajpal, MD, Clinical Team Leader  
Division of Gastroenterology Products (DGP)

**Re:** Labeling in the youngest pediatric patients

**Sponsor:** Digestive Care Inc.

**Drug:** Pertzye™ (pancrelipase)

**NDA:** 22-175

**Submission Date:** November 18, 2011  
<\\CDSESUB4\NONECTD\NDA022175\4970568>

**Indication (proposed):** treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions

**Proposed Dose:** Per CFF guidelines (See Appendix I)

**Dosage form:** delayed-release capsules

**Dosage strengths:** 8000 USP lipase units (MS-8),  
16,000 USP lipase units (MS-16)

**Route of Administration:** oral

**Consult Question:**

PMHS assistance is requested to determine if the Sponsor has provided appropriate information to provide labeling for the entire pediatric age range. Additionally, DGIEP requests assistance in developing text for an information request asking the Sponsor to clarify this issue.

**Materials Reviewed:**

- PMHS Ultresa™ Consult (May 3, 2010)
- Approved labeling Creon® (NDA 20-725), Zenpep® (NDA 22-210) and Pancreaze® (22-523)
- Type A Meeting Minutes from meeting June 22, 2011 (July 22, 2011)
- Sponsor's Proposed Labeling (November 18, 2011)
- Sponsor's proposal to fulfill PREA (November 18, 2011)
- Agency's IR (January 31, 2012) and Sponsor's Response to IR (February 10, 2012)

**Regulatory Background:**

NDA 022175, Pertzye™ (pancrelipase) delayed-release capsules for the treatment of exocrine pancreatic insufficiency due to cystic fibrosis (CF) or other conditions was initially submitted October 27, 2008 pursuant to section 505(b)(2). A Complete Response letter was issued on January 27, 2011 noting product quality, clinical pharmacology, and facility inspection deficiencies. On November 18, 2011, the Sponsor submitted a complete class 2 response to the January 2011 action letter.

The current NDA allows for the marketing of two capsule strengths, i.e. 8000 USP lipase units (MS-8), 16,000 USP lipase units (MS-16). (b) (4)

(b) (4) The Sponsor states that they intend to (b) (4) satisfy the post-approval requirement for an age-appropriate formulation for pediatric patients. During a Type A meeting with the Sponsor on June 22, 2011, the FDA communicated to the Sponsor that (b) (4)

***Reviewer Comment:***

*Given that the recommended dosing for infants is 2000-4000 lipase units per feeding or 120 ml of formula, if the development of a capsule with 2000 lipase units is feasible a capsule with this quantity of lipase may be beneficial to some pediatric patients, for example premature infants with CF.*

**PREA Requirements:**

Given that Pertzye™ and the other pancreatic enzyme products (PEPs) are considered new active ingredients, the Pediatric Research Equity Act (PREA) requires 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.

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” was requested in the Sponsor’s June 29, 2009 submission. The Sponsor stated in their November 18, 2011 submission that the pediatric requirement for pediatric patients 1 month to 1 year is not fulfilled due to the lack of an age-appropriate formulation, but that the pediatric study requirement for patients 1 year to 17 years of age has been fulfilled because the “FDA has stated in the NDA review documents of the approved competitor PEPs that the published data in the literature establish the safety and efficacy of PEPs in general for treatment of children with exocrine pancreatic insufficiency” (See Appendix II: Excerpt from the Sponsor’s November 18, 2011 Submission). The Sponsor has not requested a deferral for the development of an age-appropriate formulation and has not provided data to support that PREA is fulfilled in patients 1 year to less than 17 years.

**Reviewer Comment:**

*The Sponsor has not adequately addressed PREA in their NDA submission or resubmission. Granting a partial waiver in patients birth to 1 month based on “too few patients to study” is reasonable and consistent with the partial waivers granted for Creon®, Zenpep® and Pancreaze®.*

*The Agency has determined that the clinical experience and body of literature supporting the use of PEP products in pediatric patients are adequate to support the safety, efficacy and dosing of enteric coated PEP products in pediatric patients with CF when accompanied by data demonstrating short-term safety and efficacy in adult patients. However, although additional clinical studies may not be required in patients greater than 1 month to less than 17 years, PREA requires documentation (1) adequate to assess the safety and effectiveness of the product and (2) adequate to support dosing and administration of the product for each relevant pediatric subpopulation. Therefore, the Sponsor must provide a statement or documentation to support that the clinical trial data submitted in the NDA, and the clinical experience and body of literature supporting the use of enteric coated PEP products in pediatric patients with CF are adequate to support the safety, efficacy and dosing of Pertzye™ in patients 1 month to 17 years.*

*In addition, the Sponsor must request a deferral for an age-appropriate formulation in the population for which an age-appropriate formulation is not available. The deferral request must provide the justification and supporting documentation for the request, and the request must provide the day, month and year when the supplement for the age-appropriate formulation will be submitted to the Agency. PREA can only be considered fulfilled for those age (and weight) groups for which an age-appropriate formulation is approved (more below).*

*Please note that all partial waiver and deferral requests, and pediatric assessments must be reviewed by the Pediatric Review Committee prior to product approval.*

**Pertzye™ Proposed Labeling:**

 (b) (4)

***Dosing in Children 12 months to less than 4 years:***

*Weight based dosing is recommended by the CFF beginning at age 12 months. Patients older than 12 months and younger than 4 years are to receive starting doses of 1000*

*lipase units/kg of body weight per meal, and the recommended snack dose is half of the recommended meal dose, i.e. 500 units/kg meal. Because the smallest capsule strength of Pertzye™ is 8000 lipase units, a patient 12 months to less than 4 years must weigh at least 8 kg for Pertzye™ to provide the adequate starting meal dose for this cohort of patients. Hence, dosing for patients older than 12 months and younger than 4 years should only be provided for patients in this age cohort weighing 8 kg or more. Of note, PMHS acknowledges that to provide snack dosing for patients weighing 8 kg or more in this age cohort, half of a capsule's content would need to be administered; however, limiting approval to patients in this cohort with a minimum weight of 8 kg may limit attempts to administer smaller fractions of the capsule's content.*

**Dosing in Children 4 years and Older:**

*Because the fat content of the diet tends to decrease after age 4 years<sup>2</sup>, the recommended dose for pediatric patients older than 4 years is to begin with 500 lipase units/kg per body weight per meal, and the recommended snack dose is half of the recommended meal dose, i.e. 250 lipase units/kg/meal. For Pertzye™ to provide the adequate starting meal dose for patients 4 years and older, patients must weigh at least 16 kg. Hence, dosing for patients 4 years and older should only be provided for patients in this age cohort weighing 16 kg or more. Similar to the situation with patients 12 months to less than 4 years, PMHS acknowledges that to provide snack dosing for patients weighing 16 kg or more in this age cohort, half of a capsule's content would need to be administered; however, limiting approval to patients in this cohort with a minimum weight of 16 kg may limit attempts to administer smaller fractions of the capsule's content.*

**Conclusions and Recommendations:**

The proposed capsule strengths of Pertzye™ do not appear to (b) (4) accommodate the lipase doses recommended for infants up to age 12 months, patients older than 12 months and less than 4 years weighing less than 8 kg, and patients 4 to 17 years weighing less than 16 kg. Therefore, dosing (b) (4) should be limited to those patients for which an age-appropriate formulation is available, i.e. patients older than 12 months and less than 4 years (weighing 8 kg or more) and patients 4 years and older (weighing 16 kg or more). As discussed with the Ultresa application, providing dosing based on age and a minimum weight is recommended. In addition, labeling should note the limitations in dosing the youngest, lightest pediatric patients and state that attempting to divide a capsule's content into small fractions is not recommended.

The Sponsor has not adequately addressed PREA. A partial waiver in patients birth to one month appears appropriate and consistent with the other PEP products. A deferral for the development of an age-appropriate formulation is appropriate for patients 1 month to 12 months, patients older than one year and less than 4 years (weighing less than 8 kg), and patients 4 to 17 years (weighing less than 16 kg). The Sponsor must submit a deferral request that includes the justification and supporting documentation for the request, and the day, month and year when the supplement for the age-appropriate formulation will be submitted to the Agency. Because PREA can only be considered

fulfilled for those age (and weight) cohorts for which an age-appropriate formulation is approved, the PREA PMR cannot be considered fulfilled in the pediatric patients for which the age-appropriate formulation has been deferred, i.e. patients 1 month to 12 months, patients older than one year and less than 4 years (weighing less than 8 kg), and patients 4 to 17 years (weighing less than 16 kg).

However, if the clinical trial data submitted to the NDA demonstrate short-term safety and efficacy of Pertzye™, and the Sponsor provides a statement or documentation to support that the clinical experience and body of literature supporting the use of enteric coated PEP products in pediatric patients are adequate to support the safety, efficacy and dosing of Pertzye™ in patients 1 month to 17 years with CF, PREA may be considered fulfilled in pediatric patients greater than 1 year to less than 4 years (weighing 8 kg or more) and in patients 4 to 17 years (weighing 16 kg or more). Although the Division could consider choosing a specific age for which PREA is fulfilled and for which an age-appropriate formulation is required, given that patients with CF weigh less than otherwise healthy children,<sup>3,4</sup> and therefore choosing an age for which the Pertzye™ formulations are adequate to support dosing may be subjective and less accurate, PMHS recommends that the population for which a deferral is requested and for which PREA is considered fulfilled be specified based on age and weight.

Please note that all partial waivers and deferrals, and pediatric assessments must be reviewed by the Pediatric Review Committee before product approval.

PMHS provided assistance in developing text for the IR letter requesting (b) (4) for pediatric labeling (b) (4) (issued January 31, 2012) and the IR outlining the deficiencies in the Sponsor's proposal to address PREA. PMHS participated in the internal meeting (February 13, 2012) and Sponsor teleconference (February 22, 2012).

**APPENDIX I: PEP Dosing in Pediatric Patients (Cystic Fibrosis Foundation Guidelines<sup>1,2</sup>)**

Standard meal dosing

- Infants - 2000 to 4000 lipase units per 120 ml of formula or per breast-feeding
- Children < 4 years old – starting dose of 1000 lipase units/kg per meal
- Children > 4 years old – starting dose of 500 lipase units/kg per meal (older children tend to ingest less fat per kilogram of body weight)

Snack dosing - ½ the standard dosing

Total daily dose - should reflect approximately three meals and two or three snacks per day<sup>2</sup>. In addition, as mentioned above, to avoid fibrosing colonopathy, enzyme doses should not exceed 2500 lipase units/kg per meal, 10,000 lipase units/kg per day and 4000 lipase units/gram fat per day<sup>1</sup>.

**Appendix II:** Excerpt from Sponsor's November 18, 2011 Submission

**ADMINISTRATIVE ITEMS**

***PEDIATRIC REQUIREMENTS***

A short-term safety and efficacy of the DCI PEP were assessed in a randomized, double-blind, placebo-controlled, crossover study (Protocol 06-001) of 21 patients with exocrine pancreatic insufficiency due to cystic fibrosis, including 10 patients between 8 and 17 years of age. The safety and efficacy in 8 to 17 year old patients in this study were similar to adult patients. This information was included in the original NDA (submission dated October 27, 2008), and is hereby incorporated by cross-reference.

FDA has waived the pediatric study requirements for ages birth to 1 month, because necessary studies are impossible or highly impracticable.

The pediatric requirement for 1 month to 1 year is not fulfilled due to the lack of age appropriate formulation. FDA has deferred this requirement for the FDA approved competitor PEPs.

FDA has stated in the NDA review documents of the approved competitor PEPs, that published data in the literature establish the safety and efficacy of PEPs in general for treatment of children with exocrine pancreatic insufficiency. Therefore, DCI believes that the pediatric study requirements for its PEP have been fulfilled for ages 1 year to 17 years.

## REFERENCES

1. Borowitz D, Baker RD, Stallings V. Consensus Report on Nutrition for Pediatric Patients with Cystic Fibrosis. *Journal of Pediatric Gastroenterology and Nutrition*. 2002;35:246–259.
2. Borowitz D, Grand RF, Durie PR and the Consensus Committee. Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy. *J Peds*. 1995;127:681-84.
3. Lai H, Kosorok MR, Sondel SA, et al. Growth status in children with cystic fibrosis based on the National Cystic Fibrosis Patient Registry data: Evaluation of various criteria used to identify malnutrition. *J Pediatr*. 1998;132:478-85.
4. Powers SW, Patton SR, Byars KC, et al. Caloric Intake and Eating Behavior in Infants and Toddlers With Cystic Fibrosis. *Pediatrics* 2002;109:e75.

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/s/  
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ELIZABETH L DURMOWICZ  
03/05/2012

HARI C SACHS  
03/05/2012  
I agree with the recommendations in this consult.

LISA L MATHIS  
03/06/2012

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Label and Labeling Review**

Date: February 23, 2012

Reviewer(s): Manizheh Siahpoushan, PharmD  
Division of Medication Error Prevention and Analysis

Team Leader Zachary Oleszczuk, PharmD  
Division of Medication Error Prevention and Analysis

Division Director Carol Holquist, RPh  
Division of Medication Error Prevention and Analysis

Drug Name and Strengths: Pertzye (Pancrelipase) Delayed-release Capsules  
8,000 USP units Lipase  
(b) (4) Amylase  
Protease  
and  
16,000 USP units Lipase  
(b) (4) Amylase  
Protease

Application Type/Number: NDA 022175

Applicant/sponsor: Digestive Care, Inc

OSE RCM #: 2011-4358

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

## 1 INTRODUCTION

This review evaluates the container labels, carton labeling, Prescribing Information, and the Medication Guide for Pertzye (Pancrelipase) Delayed-release Capsules, in response to a consult from the Division of Gastroenterology Products to identify any areas of concern from a medication errors perspective.

### 1.1 REGULATORY HISTORY

This product has been marketed under the proprietary names Pancrecarb MS-4, Pancrecarb MS-8, and Pancrecarb MS-16 since 1995 as an unapproved product. A Federal Register (FR) Notice dated April 20, 2004 notified manufacturers of pancreatic insufficiency products that FDA approval, via the submission of a new drug application (NDA), would be required by April 2008 (deadline was extended to April 2010) for these products to remain in the US marketplace. In accordance to this FR notice, the manufacturer of Pertzye submitted an NDA for this product on October 27, 2008. The Applicant submitted revised labels and labeling as part of their request to review the new proposed proprietary name, Pertzye, for this product. The Applicant submitted revised labels and labeling in response to DMEPA's previous comments in OSE Review #2008-2004, dated May 8, 2009 and OSE Review #2010-441, dated June 22, 2010.

On January 27, 2011, the Agency issued a Complete Response letter for this Application due to deficiencies identified. As part of a Class-II resubmission dated November 18, 2011, the Applicant submitted draft container labels, carton labeling, Prescribing Information, and Medication Guide for review. (b) (4)

### 1.2 PRODUCT INFORMATION

The following product information is provided in the November 18, 2011 submission:

- Active Ingredient: Pancrelipase
- Indication of Use: Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions.
- Route of administration: Oral
- Dosage form: Delayed-release Capsules
- Strength: 8,000 USP units of Lipase and 16,000 USP units of Lipase. (b) (4)
- Dose and Frequency of Administration: (b) (4)  
*Children between 12 months and 4 years of age:* begin with 1,000 Lipase units/kg/meal to a maximum of 2,500 Lipase units/kg/meal (or maximum of 10,000 USP units of Lipase/kg/day), or less than 4,000 Lipase units/gram fat ingested/day; *Children 4 years and older and adults:* begin with 500 Lipase units/kg/meal to a maximum of 2,500 Lipase units/kg/meal (or maximum of

10,000 USP units of Lipase/kg/day), or less than 4,000 Lipase units/gram fat ingested per day.

- How Supplied: Supplied in bottles of (b) (4) 250
- Storage: Room temperature 20 to 25°C (68 to 77°F). Pertzeye hard gelatin capsules should be stored in a dry place in the original container.
- Container and Closure systems: The buffered Pancrelipase enteric-coated microspheres are filled into clear hard gelatin capsules that are packaged into a white high density polyethylene (HDPE) bottle, along with a (b) (4) desiccant packet, and sealed with a white (b) (4) screw cap with (b) (4) aluminum liner and induction safety seal. Each bottle is provided in a (b) (4) carton containing the full Prescribing Information and Medication Guide.

## 2 METHODS AND MATERIALS

Because Pancrelipase, the active ingredient of Pertzeye was previously marketed, DMEPA searched the FDA Adverse Event Reporting System (AERS) to identify medication errors related to the use of Pancrelipase. We also evaluated the container labels (trade and professional samples), carton labeling (trade and professional samples), Prescribing Information, and the Medication Guide for Pertzeye (Pancrelipase) Delayed-release Capsules 8,000 USP units Lipase and 16,000 USP units Lipase, and to ensure all our label and labeling recommendations in OSE Review #2010-441, dated June 22, 2010 have been implemented, and to identify areas of vulnerability that can lead to medication errors.

### 2.1 IDENTIFICATION OF MEDICATION ERRORS IN AERS DATABASE

The January 4, 2012 AERS search used the following criteria: Active ingredient ‘Pancrelipase’, Verbatim term ‘Pancrel%’ as well as the MedDRA reaction terms ‘Medication Errors’ (HLGT), ‘Product Label Issues’ (HLT), and ‘Product Quality Issue’ (PT). The date limit was set from October 7, 2011 (the date of the last search conducted in OSE review #2011-3389, dated November 1, 2011) to January 4, 2012. Those cases not pertaining to errors, pertaining to errors of concomitant drugs, and occurrence of adverse events not due to medication errors were excluded from further analysis.

### 2.2 LABELS AND LABELING

Using failure Mode and Effects Analysis<sup>1</sup>, the principles of human factors, and the lessons learned from postmarketing experience, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the container labels (trade and professional samples), carton labeling (trade and professional samples), Prescribing Information, and Medication Guide, submitted on November 18, 2011, to identify vulnerabilities that may lead to medication errors. The following were submitted for our evaluation (see Appendices A through C):

(b) (4)

- Container labels and carton labeling for the 100 count and 250 count trade (8,000 USP units Lipase, and 16,000 USP units Lipase) submitted on 11/18/11
- Prescribing Information submitted on 11/18/11

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004

- Medication Guide submitted on 11/18/11

### 3 RESULTS

The following sections describe the results of DMEPA's medication error searches and label and labeling evaluation.

#### 3.1 IDENTIFICATION OF MEDICATION ERRORS IN AERS DATABASE RESULTS

The January 4, 2012 AERS search did not identify any cases.

#### 3.2 LABELS AND LABELING RISK ASSESSMENT

Our evaluation of the container labels, carton labeling, Prescribing Information, and the Medication Guide noted that the Applicant did not implement most of DMEPA's recommendations from OSE review #2010-441, dated June 22, 2010. However, it is possible that because of the deficiencies identified in their submission, which resulted in Complete Responses, the label and labeling comments were deferred until the Application was adequate. The deficiencies identified include:

- The proposed proprietary name is presented in all capital letters which decreases readability.
- In accordance with 21 CFR 201.10(g)(2), the established name is not at least half the size of the proprietary name.
- In accordance with 21 CFR 201.10(d)(1), a statement of the quantity of an ingredient that expresses the quantity of the ingredient in each capsule does not appear on the carton and container labels.
- The warning statement (b) (4) contains negative language which may be overlooked by patients and have the opposite effect of the intended meaning.
- The dosage form, Delayed-release Capsules, Bicarbonate-Buffered and Enteric-Coated Microspheres' is not recognized by the USP.
- The dosage form, Delayed-release Capsules lacks prominence.
- The company logo on the principal display panel of container labels and carton labeling is too prominent and can distract from other important information such as the product strength.

(b) (4)

### 4 CONCLUSIONS

Our evaluation of the proposed labels and labeling identified areas of needed improvement in order to reduce the potential for medication errors. We provide recommendations to the Prescribing Information in Section 4.1 *Comments to the Division* for discussion during the labeling meetings. Section 4.2 *Comments to the Applicant* for the container labels and carton labeling. We request the recommendations in Section 4.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact OSE Regulatory Project Manager, Nitin Patel, at 301-796-5412.

#### 4.1 COMMENTS TO THE DIVISION

##### A. General Comments

1. The dosage form “Delayed-Release Capsules, Bicarbonate-Buffered and Enteric-Coated Microspheres” is not recognized by the USP. We recommend that this dosage form be revised to a dosage form that is recognized by CDER and USP. We defer the appropriate dosage form to the CMC reviewer.

2.

(b) (4)

##### B. Full Prescribing Information- Dosage and Administration

In the Administration Section, under *Children and Adults*, revise the statement,

(b) (4)

**to read ‘Pertzye capsules should be swallowed whole. Do not crush or chew the capsules and capsule contents.’** As currently presented, the warning statement begins with negative language which may be overlooked and have the opposite effect of the intended meaning.

##### C. Full Prescribing Information- Storage and Handling

We recommend not using the hyphen between the numbers because a hyphen can be misinterpreted as a negative sign. Therefore, please revise 20-25°C (68-77°F) and 15-40°C (59-104°F) to read 20°C to 25°C (68°F to 77°F) and 15°C to 40°C (59°F to 104°F).

##### D. Medication Guide

Revise the fourth bullet point under ‘How should I take Pertzye?’ to begin with positive language. The revised statement may appear as follows: **‘Pertzye**

**capsules should be swallowed whole. Do not crush or chew the capsules and capsule contents, and do not hold the capsule or contents in your mouth.'**

#### 4.2 COMMENTS TO THE APPLICANT

##### A. General Comments For Container Labels and Carton Labeling

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 by the Applicant, 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 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.

## **5 REFERENCES**

### **1. ADVERSE EVENTS REPORTING SYSTEM (AERS)**

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufacturers that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential post marketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

### **2. PREVIOUS OSE REVIEW**

OSE Review #2011-3389, Ultresa Label and Labeling Review, Siahpoushan, M, November 1, 2011.

OSE Review #2010-441, Pertzye Label and Labeling Review, Chan, I.Z., June 22, 2010.

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MANIZHEH SIAHPOUSHAN  
02/23/2012

ZACHARY A OLESZCZUK  
02/23/2012

CAROL A HOLQUIST  
02/23/2012

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** December 9, 2010

**To:** Matthew Scherer, Regulatory Health Project Manager  
Division of Gastroenterology Products (DGP)

**From:** Kathleen Klemm, Regulatory Review Officer  
Cynthia Collins, Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications (DDMAC)

**CC:** Lisa Hubbard, Professional Group Leader  
Shefali Doshi, Acting Direct-To-Consumer Group Leader  
Michael Wade, Regulatory Project Manager  
DDMAC

**Subject:** NDA 022175  
  
DDMAC labeling comments for Pertzye (pancrelipase)

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We acknowledge receipt of your September 23, 2010, consult request for the proposed package insert (PI), carton/container labeling, and Medication Guide for Pertzye. DDMAC was notified by DGP on December 9, 2010, that labeling negotiations would not be initiated during the current review cycle and that a Complete Response letter would be issued. Therefore, DDMAC will provide comments regarding labeling for this application during a subsequent review cycle. DDMAC requests that DGP submit a new consult request during the subsequent review cycle.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions regarding the PI or carton/container labeling, please contact Kathleen Klemm at 301.796.3946 or [Kathleen.Klemm@fda.hhs.gov](mailto:Kathleen.Klemm@fda.hhs.gov). If you have any questions regarding the Medication Guide, please contact Cynthia Collins at 301.796.4284 or [Cynthia.Collins@fda.hhs.gov](mailto:Cynthia.Collins@fda.hhs.gov).

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/s/  
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KATHLEEN KLEMM  
12/09/2010



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: June 22, 2010

To: Donna Griebel, M.D., Director  
Division of Gastroenterology Products

Through: Melina Griffis, RPh, Team Leader  
Denise Toyer, Pharm.D., Deputy Director  
Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis (DMEPA)

From: Irene Z. Chan, Pharm.D., BCPS, Safety Evaluator  
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name(s): Pertzye (Pancrelipase) Delayed-Release Capsules  
[REDACTED] (b) (4)

Lipase 8,000 USP Units [REDACTED] (b) (4)

Lipase 16,000 USP Units [REDACTED] (b) (4)

Application Type/Number: NDA 022175

Applicant: Digestive Care, Inc.

OSE RCM #: 2010-441

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## **1 INTRODUCTION**

This review summarizes the Division of Medication Error Prevention and Analysis' (DMEPA) evaluation of the revised labels and labeling for Pertzye contained in the Applicant's proprietary name request submission, dated March 25, 2010, for areas of vulnerability that can lead to medication errors. We provide recommendations in Section 4 that aim at reducing the risk of medication errors with regard to the proposed product labels and labeling.

### **1.1 REGULATORY HISTORY**

This product has been marketed under the proprietary names Pancrecarb MS-4, Pancrecarb MS-8, and Pancrecarb MS-16 since 1995 as an unapproved product. A Federal Register (FR) Notice dated April 20, 2004 notified manufacturers of pancreatic insufficiency products that FDA approval, via the submission of a new drug application (NDA), would be required by April 2008 (deadline has been extended to April 2010) for these products to remain in the US marketplace. In accordance to this FR notice, the manufacturer of Pertzye submitted an NDA for this product on October 27, 2008. The Applicant submitted revised labels and labeling as part of their request to review the new proposed proprietary name, Pertzye, for this product. The Applicant submitted revised labels and labeling in response to the Division of Medication Error Prevention and Analysis' previous comments (see OSE review #2008-2004 dated May 8, 2009).

## **2 METHODS AND MATERIALS**

### **2.1 FDA ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE**

Pancrecarb capsules are currently marketed; therefore, DMEPA conducted a search of the FDA Adverse Event Reporting System (AERS) database on March 18, 2010, to identify medication errors involving Pancrecarb.

The MedRA High Level Group Terms (HLGT) "Medication Errors" and "Product Quality Issues" were used as search criteria for Reactions. The search criteria used for Products was verbatim substance search "Pancrec%". No date limitations were set.

### **2.2 LABEL AND LABELING**

Using Failure Mode and Effects Analysis (FMEA), the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the labels and labeling submitted as part of the March 25, 2010 submission (see Appendices A through F). Additionally, we compared the revised labels and labeling to the labels and labeling contained in the December 4, 2008 proprietary name submission and to the recommendations we made in OSE review # 2008-2004 to ensure all recommendations were incorporated.

## **3 RESULTS**

### **3.1 FDA ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE**

The AERS search conducted on March 18, 2010, yielded no cases.

### **3.2 LABEL AND LABELING**

The label and labeling risk assessment findings indicate the presentation of information on the proposed labels and labeling introduces vulnerability to confusion that can lead to medication errors. These conclusions and their corresponding recommendations are further explained in Section 4 below.

## 4 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation of the proposed container labels and insert labeling noted areas of needed improvement in order to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 4.1 Comments to the Division. We request the recommendations for the container labels and carton labeling in Section 4.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Nitin Patel, at 301-796-5412.

### 4.1 COMMENTS TO THE DIVISION

#### A. GENERAL COMMENTS

The dosage form is listed as Delayed-Release Capsules, Bicarbonate-Buffered and Enteric-Coated Microspheres. Since this dosage form is not recognized by the USP, it is currently under review by the CMC reviewer. We defer the appropriate designation of the dosage form to the CMC reviewer.

#### B. HIGHLIGHTS OF PRESCRIBING INFORMATION

Throughout this section there is reference to (b) (4). In instances where appropriate, we recommend replacing these terms with the words *capsule contents* or *capsule* as appropriate to avoid confusion and maintain consistency throughout the insert labeling.

#### C. FULL PRESCRIBING INFORMATION – Dosage Forms and Strengths

In order to be consistent with the approved labeling for Zenpep, consider revising the statement (b) (4) to read as follows:

*PERTZYE is available in (b) (4) color coded capsule strengths. Other active ingredients include protease and amylase. Each PERTZYE capsule strength contains the specified amounts of lipase, protease, and amylase.*

*Capsules of all strengths have a circular stripe on the capsule body and are colored as follows:*

#### D. FULL PRESCRIBING INFORMATION – Storage and Handling

In order to be consistent with the approved labeling for Zenpep, consider adding the statement, *DO NOT CRUSH PERTZYE delayed-release capsules.*

### 4.2 COMMENTS TO THE APPLICANT

#### A. GENERAL COMMENTS FOR LABELS AND LABELING

1. 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.

2. The 100 count and 250 count bottles can be (b) (4) Please assure these bottles utilize child-resistant closures to comply with the Poison Prevention Packaging Act of 1970.

B. CONTAINER LABELS AND CARTON LABELING FOR (b) (4) 100 COUNT, AND 250 COUNT BOTTLES ( (b) (4)  
8,000 U.S.P. Units lipase/ (b) (4)  
16,000 U.S.P. Units lipase (b) (4)

1. In accordance with 21 CFR 201.10(d)(1), ensure that any statement of the quantity of an ingredient expresses the quantity of the ingredient in each capsule. Therefore, add a statement such as, *Each capsule contains X USP Units of lipase, X USP Units of amylase, and X USP Units of protease.*
2. As currently presented, the graphic of a capsule with the lipase strength enclosed is placed between the established name and the strength presentation. Remove the entire graphic.
3. The statement located on the side panels of the container labels which reads: (b) (4) should be revised (and changed back to the previous bolded font) as follows:

**Pertzye capsules and capsule contents should not be crushed or chewed.**

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

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/s/

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IRENE Z CHAN  
06/22/2010

MELINA N GRIFFIS  
06/23/2010

DENISE P TOYER  
06/23/2010

CAROL A HOLQUIST  
06/23/2010

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**CLINICAL INSPECTION SUMMARY**

**DATE:** June 25, 2009

**TO:** Elizabeth Ford, Regulatory Project Manager  
Marjorie Dannis, M.D., Medical Officer  
Division of Gastroenterology Products

**FROM:** Roy Blay, Ph.D.  
Good Clinical Practice Branch 1  
Division of Scientific Investigations

**THROUGH:** Constance Lewin, M.D., M.P.H.  
Branch Chief  
Good Clinical Practice Branch 1  
Division of Scientific Investigations

**SUBJECT:** Evaluation of Clinical Inspections.

**NDA:** 22-175

**APPLICANT:** Digestive Care, Inc.

**DRUG:** Pancrecarb

**NME:** No

**THERAPEUTIC CLASSIFICATION:** Standard Review

**INDICATION:** Exocrine pancreatic insufficiency

**CONSULTATION REQUEST DATE:** December 19, 2008

**DIVISION ACTION GOAL DATE:** August 27, 2009

**PDUFA DATE:** August 27, 2009

## I. BACKGROUND:

The conduct of protocol #06-001 entitled “A Randomized, Double-Blind, Placebo-Controlled, Multi-Center, Crossover Study to Evaluate the Effectiveness and Safety of PANCRECARB MS-16 (pancrelipase) in Reducing Steatorrhea in Children and Adults with Cystic Fibrosis” was inspected.

The sites of Drs. Strausbaugh (site 007) and Ahrens (site 191) were both selected for inspection because they had large percentages of subjects completing the study. In addition, site 007 had the highest mean change in the coefficient of fat absorption (%CFA).

The primary objective was to determine the efficacy and safety of PANCRECARB® MS-16 (pancrelipase) in reducing steatorrhea (as measured by 72-hour stool fat determinations) in children and adults with cystic fibrosis (CF) and exocrine pancreatic insufficiency (EPI).

## II. RESULTS (by Site):

Name of CI, Location	Protocol #:/ # of Subjects/	Inspection Dates	Final Classification
Steven D. Strausbaugh, M.D. 11100 Euclid Avenue Cleveland, OH 44106-1716	06-001/ 6	17-25 Feb 09	NAI
Richard Ahrens, M.D. 200 Hawkins Drive University of Iowa Hospitals & Clinic Iowa City, IA 52242	06-001/ 5	3-5 Mar 09	NAI

### Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field;  
EIR has not been received from the field and complete review of EIR is pending.

### 1. Steven D. Strausbaugh, M.D.

11100 Euclid Avenue  
Cleveland, OH 44106-1716

**a. What was inspected:** Six of seven randomized subjects completed the study. Six subject records were reviewed in depth including calculations of the percent changes in the coefficients of fat and nitrogen absorption (%CFA and %CNA, respectively). The %CFA served as the primary efficacy variable for this study. Records reviewed included, but were not limited to, food diaries, consent/assent forms, calculations of consumption of fats, protein and carbohydrates, test article dosing, and adverse event reporting.

**b. General observations/commentary:** Review of the records noted above revealed no significant discrepancies/regulatory violations.

**c. Assessment of data integrity:** Data appear acceptable in support of the respective application.

2. Richard Ahrens, M.D.  
200 Hawkins Drive  
University of Iowa Hospitals & Clinic  
Iowa City, IA 52242

**a. What was inspected:** Seven subjects were enrolled in the study with five completing the study. Records reviewed for all seven subjects included informed consent, eligibility criteria, test article accountability, blinding and randomization, adverse events, study discontinuation, and concomitant medications. The primary efficacy variable for this study, %CFA, was verified.

**b. General observations/commentary:** Review of the records noted above revealed no significant discrepancies/regulatory violations.

**c. Assessment of data integrity:** Data appear acceptable in support of the respective application.

### III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data generated by the clinical sites of Drs. Strausbaugh and Ahrens appear acceptable in support of the respective application.

*{See appended electronic signature page}*

Roy Blay, Ph.D.  
Good Clinical Practice Branch I  
Division of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Constance Lewin, M.D., M.P.H.  
Branch Chief  
Good Clinical Practice Branch I  
Division of Scientific Investigations

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/s/

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Roy Blay  
6/26/2009 09:43:39 AM  
CSO

Constance Lewin  
6/26/2009 09:48:49 AM  
MEDICAL OFFICER



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: May 8, 2009

To: Donna Griebel, MD, Director  
Division of Gastroenterology Products

Through: Denise Toyer, Pharm D., Deputy Director  
Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis

From: Melina Griffis, RPh, Acting Team Leader  
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): PANCRECARB<sup>®</sup> (Pancrelipase) Delayed Release Capsules

Application Type/Number: NDA 22-175

Applicant/sponsor: Digestive Care

OSE RCM #: 2008-2004

## EXECUTIVE SUMMARY

This review is in response to a request from the Division of Gastroenterology Products for an assessment of the labels and labeling for the product, Pancrecarb (NDA 22-175) for evaluation to identify areas that could lead to medication errors. Using Failure Mode and Effects Analysis<sup>1</sup> and lessons learned from post-marketing experience with the pancrelipase products, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the container labels, carton labeling and insert labeling.

Our findings indicate that the presentation of information in the labels and labeling introduces vulnerability to confusion that could lead to medication errors. We provide recommendations in section 2.1 below that aim at reducing the risk of medication errors and provide consistent recommendations for labeling of the pancrelipase products.

### 1 MATERIALS REVIEWED

For this product the Applicant submitted labels and labeling as part of the December 4, 2008 proprietary name submission. (Appendix A for images)

### 2 RECOMMENDATIONS

We request the following recommendations be communicated to the Applicant prior to approval. We would be willing to meet with the Division for further discussion if needed. If you have further questions or need clarifications, please contact Nina Ton, project manager at 301-796-1648.

#### 2.1 COMMENTS TO THE APPLICANT

##### A. *All Labels and Labeling*

As conveyed previously in our letter dated April 8, 2009, the proposed [REDACTED] (b) (4) [REDACTED] are inappropriate and should be removed.

##### B. *Container Labels*

1. The size and prominence of the ingredients and strengths should be increased. Additionally, we recommend that you box this section on the principle display panel so as to clearly differentiate (through the use of colors, shading, highlighting or some other means) between the [REDACTED] (b) (4) product strengths for the following reasons:

The “each capsule contains...” portion of the label containing the 3 active ingredients and their respective strengths will represent the product strength on the principle display panel. Although presently the 3 ingredients and their respective strengths are listed, this alone will not distinguish the product strengths from one another. Based on postmarketing experience, labels and labeling that are not adequately differentiated increase the risk of confusion and also contribute to product selection errors that can lead to an over or under dose because the wrong strength is dispensed and administered. In addition, the 3 ingredients should appear immediately after the established name and dosage form statements.

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

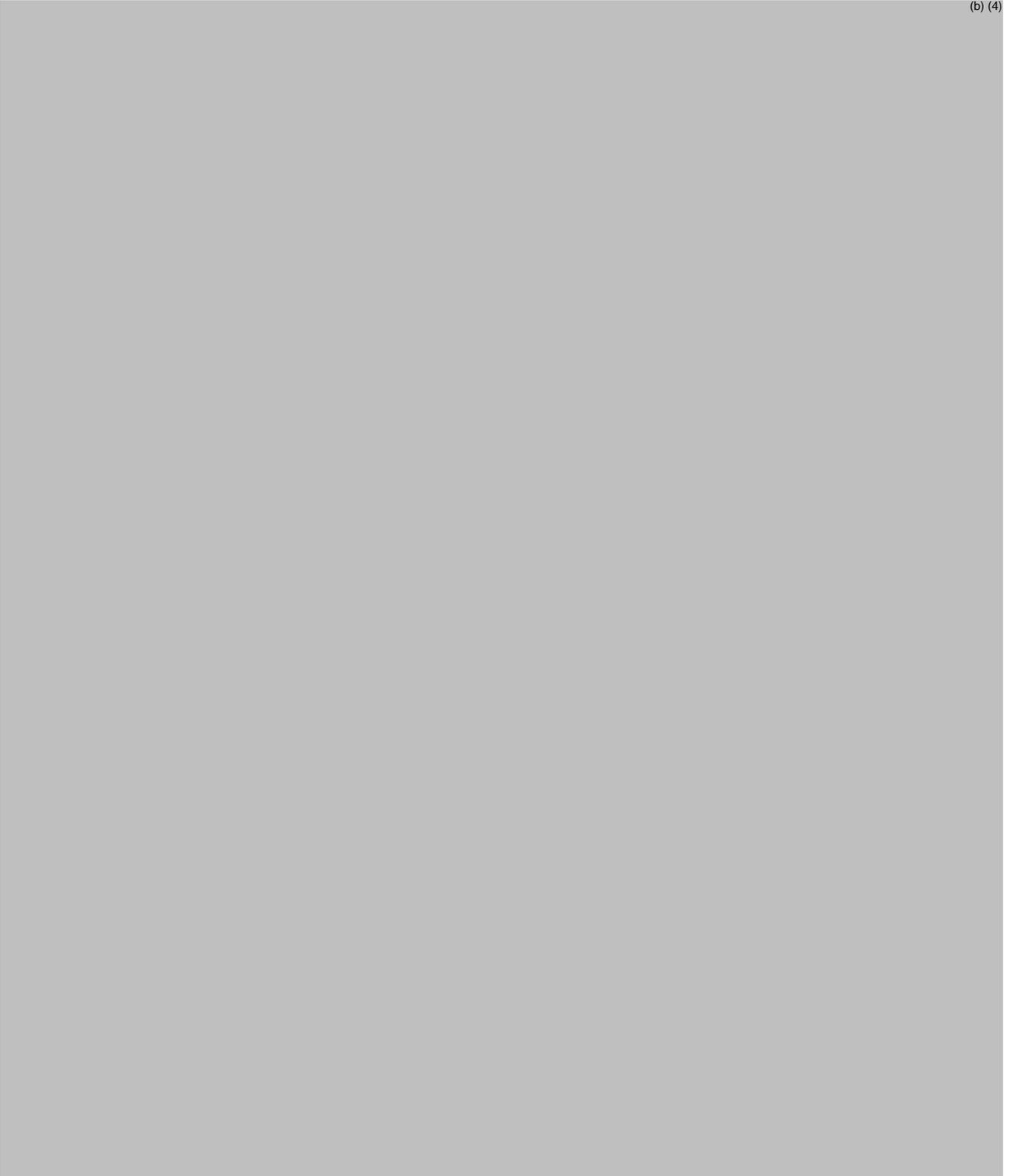
2. Revise the established name so that it is at least ½ the size of the proprietary name to be in accordance with 21CFR 201.10(g)(2).
3. Remove the statement [REDACTED] (b) (4) from the principle display panel since these terms do not convey any relevant information about the product.
4. Replace the term [REDACTED] (b) (4) with ‘capsule contents’ or ‘capsules’ as appropriate on the side panel labels.
5. The statement located on the side panels of the container labels which reads: [REDACTED] (b) (4) should be revised (and remain bolded) as follows:  
*“Pancrecarb capsules and capsule contents should not be crushed or chewed.”*
6. Remove the graphic depiction of a capsule containing the Pancrecarb name. A less prominently displayed picture of the actual capsule would be acceptable.
7. Relocate the capsule quantity statement to the bottom 1/3 of the label.
8. Include a statement on the principle display panel informing patients and healthcare practitioners that Pancrecarb is dosed based on lipase units.
9. Include a statement alerting the dispenser to provide a Medication Guide for all strengths. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):
  1. “Dispense the enclosed Medication Guide to each patient.” Or
  2. “Dispense the accompanying Medication Guide to each patient.”
10. Sufficient numbers of Medication Guides should be provided with the product such that a dispenser can provide one Medication Guide with each new or refilled prescription. We recommend that each packaging configuration contain enough Medication Guides so that one is provided for each “usual” or average dose. For example:
  1. A minimum of four Medication Guides would be provided with a bottle of 100 for a product where the usual or average dose is 1 capsule/tablet daily, thus a monthly supply is 30 tablets.
  2. A minimum of one Medication Guide would be provided with unit of use where it is expected that all tablets/capsules would be supplied to the patient.

**C. Insert Labeling**

Throughout the labeling there is reference to [REDACTED] (b) (4) [REDACTED]. These statements should be removed. In instances where appropriate it could be replaced with the word ‘capsule contents’ or ‘capsule’ as appropriate.

**APPENDICES**

(b) (4)



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/s/

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Melina Griffis  
5/8/2009 02:32:13 PM  
DRUG SAFETY OFFICE REVIEWER

Denise Toyer  
5/8/2009 04:28:08 PM  
DRUG SAFETY OFFICE REVIEWER

**NDA/BLA REGULATORY FILING REVIEW**  
(Including Memo of Filing Meeting)

<b>Application Information</b>		
NDA # 22175 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Pancrecarb Established/Proper Name: pancrelipase Dosage Form: capsule Strengths: <sup>(b)(4)</sup> 8000, 16000 USP units of lipase		
Applicant: Digestive Care, Inc. Agent for Applicant (if applicable):		
Date of Application: 27 October 2008 Date of Receipt: 27 October 2008 Date clock started after UN:		
PDUFA Goal Date: 27 August 2009	Action Goal Date (if different):	
Filing Date: 26 December 2008 Date of Filing Meeting: 21 November 2008		
Chemical Classification: (1,2,3 etc.) (original NDAs only) 7		
Proposed Indication(s): Exocrine pancreatic insufficiency		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)	
<i>Refer to Appendix A for further information.</i>	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
Review Classification:  <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>  <i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical disease Priority review voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/> Resubmission after refuse to file? <input type="checkbox"/>		
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input checked="" type="checkbox"/> Fast Track <input checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)	

Collaborative Review Division (if OTC product):	
List referenced IND Number(s): IND 45223	
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>Application Integrity Policy</b>	
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> <a href="http://www.fda.gov/ora/compliance_ref/aiplist.html">http://www.fda.gov/ora/compliance_ref/aiplist.html</a>  If yes, explain:  If yes, has OC/DMPQ been notified of the submission?  Comments:	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>User Fees</b>	
Form 3397 (User Fee Cover Sheet) submitted	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
User Fee Status  Comments:	<input type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input checked="" type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i>	
<b>Exclusivity</b>	
Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at:</i> <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a>  If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p><b>Comments:</b></p>	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> YES # years requested: <input checked="" type="checkbox"/> NO</p>
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>):</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<p><input checked="" type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b>	
<p>1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p> <p>2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).</p> <p>3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?</p> <p><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p>	<p><input type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>

<p>4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <i>Check the Electronic Orange Book at: <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a></i></p>		<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO	
<p>If yes, please list below:</p>			
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>			
<p><b>Format and Content</b></p>			
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p> <p><b>Comments:</b></p>		<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input type="checkbox"/> CTD <input checked="" type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)	
<p><b>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</b></p>			
<p><b>If electronic submission:</b>  <u>paper</u> forms and certifications signed (non-CTD) or <u>electronic</u> forms and certifications signed (scanned or digital signature)(CTD)?</p> <p><i>Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p> <p><b>Comments:</b> Submitted in an amendment dated 12 DEC 2008, received 15 DEC 2008.</p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	
<p><b>If electronic submission, does it follow the eCTD guidance?</b>  (<a href="http://www.fda.gov/cder/guidance/7087rev.pdf">http://www.fda.gov/cder/guidance/7087rev.pdf</a>)</p> <p><b>If not, explain (e.g., waiver granted):</b> <u>Waiver granted</u> (by Virginia Ventura of the FDA, in electronic correspondence dated 4 March 2008 to Eve Damiano of Digestive Care, Inc.)</p>		<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO	

<p><b>Form 356h:</b> Is a signed form 356h included?</p> <p><i>If foreign applicant, <b>both</b> the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input type="checkbox"/> legible  <input type="checkbox"/> English (or translated into English)  <input type="checkbox"/> pagination  <input type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>Controlled substance/Product with abuse potential:</b></p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>BLAs/BLA efficacy supplements only:</b></p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p><b>If yes, BLA #</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	
<p>Patent information submitted on form FDA 3542a?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Debarment Certification</b>	
<p>Correctly worded Debarment Certification with authorized signature?</p> <p><i>If foreign applicant, <b>both</b> the applicant and the U.S. Agent must</i></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><b>sign the certification.</b></p> <p><i>Note: Debarment Certification should use wording in FD&amp;C Act section 306(k)(1) i.e., “[Name of applicant] 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.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p> <p><b>Comments:</b></p>	
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	
<p>Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>)</p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<p><input checked="" type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>)</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<b>Financial Disclosure</b>	
<p>Financial Disclosure forms included with authorized signature?</p> <p><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<b>Pediatrics</b>	
<p><b><u>PREA</u></b></p>	
<p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	
<p>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES</p> <p><input checked="" type="checkbox"/> NO</p>
<p><b>If no</b>, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p> <ul style="list-style-type: none"> <li>• <i>If no, request in 74-day letter.</i></li> <li>• <b>If yes</b>, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</li> </ul>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p><b>Comments:</b> Certification included, but document not signed.</p>	

<b>BPCA (NDAs/NDA efficacy supplements only):</b>	
Is this submission a complete response to a pediatric Written Request?  <i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i>  <b>Comments:</b>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>Prescription Labeling</b>	
Check all types of labeling submitted.  <b>Comments:</b>	<input type="checkbox"/> Not applicable <input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use <input type="checkbox"/> MedGuide <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)
Is electronic Content of Labeling submitted in SPL format?  <i>If no, request in 74-day letter.</i>  <b>Comments:</b>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Package insert (PI) submitted in PLR format?  <b>If no</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If before</b> , what is the status of the request?  <i>If no, request in 74-day letter.</i>  <b>Comments:</b>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?  <b>Comments:</b>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
MedGuide or PPI (plus PI) consulted to OSE/DRISK? ( <i>send WORD version if available</i> )  <b>Comments:</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
REMS consulted to OSE/DRISK?  <b>Comments:</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<b>OTC Labeling</b>	
<p>Check all types of labeling submitted.</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> <b>Not Applicable</b> <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)
<p>Is electronic content of labeling submitted?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Are annotated specifications submitted for all stock keeping units (SKUs)?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>If representative labeling is submitted, are all represented SKUs defined?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?</p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Meeting Minutes/SPA Agreements</b>	
<p>End-of Phase 2 meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO
<p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p><b>Comments:</b> 23 June 2005, 11 September 2006, 5 February 2007, 31 October 2007</p>	<input checked="" type="checkbox"/> YES Date(s): <input type="checkbox"/> NO
<p>Any Special Protocol Assessment (SPA) agreements?</p> <p><i>If yes, distribute letter and/or relevant minutes before filing meeting.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** 21 November 2008

**NDA/BLA #:** 22-175

**PROPRIETARY/ESTABLISHED NAMES:** Pancrecarb/pancrelipase

**APPLICANT:** Digestive Care, Inc.

**BACKGROUND:** NDA 22-175/Pancrecarb (pancrelipase) is a Type 7, NCE pancreatic drug, indicated for the treatment of exocrine pancreatic insufficiency. This NDA is submitted in accordance with the Federal Register (FR) Notice dated April 28, 2004, which announced that all exocrine pancreatic insufficiency drugs (pancreatic drugs) are new drugs under Section 201(p) of the Federal Food Drug and Cosmetic Act.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Elizabeth Ford, R.N.	Y
	CPMS/TL:	Brian Strongin, R.Ph., M.B.A.	Y
Cross-Discipline Team Leader (CDTL)			
Clinical	Reviewer:	Marjorie Dannis, M.D.	Y
	TL:	Anil Rajpal, M.D.	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
Labeling Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
OSE	Reviewer:		
	TL:		
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Tien Mien Chen, Ph.D.	Y
	TL:	Sue Chih Lee, Ph.D.	N
Biostatistics	Reviewer:	Freda Cooner, Ph.D.	Y
	TL:	Mike Welch, Ph.D.	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Tamal Chakraborti, Ph.D.	Y
	TL:	Sushanta Chakder, Ph.D.	Y
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Wei Guo, Ph.D.	Y
	TL:	Emanuela Lacana, Ph.D.	Y
Facility ( <i>for BLAs/BLA supplements</i> )	Reviewer:		
	TL:		
Microbiology, sterility ( <i>for NDAs/NDA efficacy supplements</i> )	Reviewer:	Vinayak Pawar, Ph.D.	N
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Other reviewers	ONDQA Dissolution reviewer: assignment pending		

**OTHER ATTENDEES:** Anne Pariser M.D., Joyce Korvick M.D., Kristen Everett R.N.

505(b)(2) filing issues?  <b>If yes, list issues:</b>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
Per reviewers, are all parts in English or English translation?  <b>If no, explain:</b>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><b>Electronic Submission comments</b></p> <p><b>List comments:</b> Rolling Review submission. Each submission has a table of contents, but there isn't one comprehensive table of contents to include both submissions.</p>	<input type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b> Potential RTF issues related to ISS/ISE, and electronic data sets. RPM to schedule t-con with company before 11/26.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no</b>, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input checked="" type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason: The proposed product contains diethyl phthalate and is slightly toxic at very high doses.
<ul style="list-style-type: none"> <li>If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b> Microbiologist not present at meeting</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter

<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> <li>• Sterile product?</li> </ul> <p><b>If yes, was Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</b></p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>FACILITY (BLAs only)</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>REGULATORY PROJECT MANAGEMENT</b>	
<p><b>Signatory Authority:</b> Julie Beitz, M.D., Director, Office of Drug Evaluation III</p> <p><b>GRMP Timeline Milestones:</b>  Filing: 26 Dec 2008;  74 Day Letter: 09 Jan 2009  Mid-cycle: 5 Mar 2009  Wrap-up: 22 Jun 2009  Target Date: 13 July 2009  PDUFA Goal Date: 27 August 2009</p> <p><b>Comments:</b></p>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <ul style="list-style-type: none"> <li><input type="checkbox"/> No review issues have been identified for the 74-day letter.</li> <li><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</li> <li><input checked="" type="checkbox"/> Standard Review</li> <li><input type="checkbox"/> Priority Review</li> </ul>
<b>ACTIONS ITEMS</b>	
<input checked="" type="checkbox"/>	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
<input type="checkbox"/>	If filed and the application is under AIP, prepare a letter either granting (for signature by

	Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If BLA or priority review NDA, send 60-day letter.
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Other: Set up teleconference with the applicant to discuss Clinical issues, Revisions required to 356h, debarment certification, table of contents, and location of SPL.

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original 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) 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, or
- (3) 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) 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, and.
- (3) 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) 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, or
- (3) 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 OND ADRA or OND IO.

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/s/

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Elizabeth A Ford  
12/19/2008 04:16:13 PM  
CSO

# **REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)**

## **Division of Gastroenterology Products**

**Application Number:** NDA 22-175

**Name of Drug:** Pancrecarb (pancrelipase) Capsules

**Applicant:** Digestive Care, Inc.

### **Material Reviewed:**

**Submission Date(s):** 27 October 2008

**Receipt Date(s):** 27 October 2008

**Submission Date of Structure Product Labeling (SPL):** 27 October 2008

**Type of Labeling Reviewed:** SPL

### **Background and Summary**

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

### **Review**

The following issues/deficiencies have been identified in your proposed labeling.

#### **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.

## **Recommendations**

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

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

Supervisory Comment/Concurrence:

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Brian K. Strongin, R.Ph., M.B.A.  
Chief, Project Management Staff

Drafted: EASF/9 Dec 2008

Revised/Initialed: BKS/12 Dec 2008

Finalized: EASF/18 Dec 2008

Filename: CSO Labeling Review Template (updated 1-16-07).doc

**CSO LABELING REVIEW OF PLR FORMAT**

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/s/

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Elizabeth A Ford  
12/18/2008 01:57:10 PM  
CSO

Brian Strongin  
12/18/2008 02:29:08 PM  
CSO