

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-175Orig1s000

CHEMISTRY REVIEW(S)

SUMMARY NDA22175 Pertzye



DEPARTMENT OF HEALTH & HUMAN SERVICES

Center for Drugs Evaluation and Research – Food and Drug Administration
Office of Biotechnology Products / Office of Pharmaceutical Science
Division of Therapeutic Proteins

The Quality Team Leader's Executive Summary

From: Emanuela Lacana, PhD
Division of Therapeutic proteins (DTP)

Through: Amy Rosenberg, MD
Division Director, DTP

NDA Number: 22175
Product: Pertzye
Sponsor: Digestive Care, Inc.

Date of Review: 15 May, 2012
Due Date of CDTL Memo: 27 April, 2012

I. RECOMMENDATIONS AND CONCLUSIONS ON APPROVABILITY

The Division of Therapeutic Proteins, Office of Biotechnology Products, OPS, CDER, recommends approval of NDA 22175 for Pertzye (pancrelipase) manufactured by Digestive Care, Inc (DCI). The data submitted in this application are adequate to support the conclusion that the manufacture of Pertzye is well controlled, and leads to a product that is safe and potent. It is recommended that this product be approved for human use (under conditions specified in the package insert).

II. POST MARKETING COMMITMENTS/POST MARKETING REQUIREMENTS

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

Final Report Submission by September 1, 2012

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

Final Report Submission by March 1, 2013

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

Final Report Submission by March 1, 2013

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

Final Report Submission by May 15, 2013

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

Final Report Submission by April 15, 2013

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

Final Report Submission by June 1, 2012

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

Final Report Submission by March 15, 2013

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

Final Report Submission by June 1, 2012

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

Final Report Submission by May 15, 2013

Drug Product PMCs:

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

Final Report Submission by December 2015

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

Final Protocol Submission by July 2012

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

Final Report Submission by July 2015

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

Final Report Submission by December 2012

EXECUTIVE SUMMARY

This summary covers the responses provided by the firm to the Complete Response letter issued January 27, 2011. Detailed description of drug substance and drug product, product quality control and stability, and conditions of use were covered in the TL memo attached to Dr. Wei Guo's primary review, uploaded in DARRTS on August 25, 2009. The reviewer identified several issues that precluded approval of the NDA at that time. DCI resubmitted the NDA on August 21, 2010. The resubmission did not adequately address all the issues identified in the previous review and the NDA was not approved. The content of the resubmission and issues precluding approval were covered in the TL memo uploaded in DARRTS on January 21, 2011.

The complete response issues related to the drug substance (pancrelipase) and drug substance manufacturer (b) (4) as well as to drug product as summarized below:

Regarding drug substance:

1. *Bacillus cereus* and its enterotoxin were detected in samples of drug substance collected by FDA investigators during the inspection of the manufacturing site. The sponsor and drug substance manufacturer had not adequately addressed this issue during the review cycle.
2. (b) (4) had inadequate bioburden control, in terms of incoming raw materials and cleaning procedures.
3. (b) (4) introduced changes in the manufacturing process of the drug substance that were not submitted in the DMF. Specifically, (b) (4) switched from (b) (4) to (b) (4) intermediate storage containers without performing extractable/leachable studies.
4. (b) (4) received an unfavorable inspection report that resulted in (b) (4) a "withhold recommendation" from the Office of Compliance.

Regarding drug product:

1. The sponsor did not provide a prospective process validation protocol and validation reports.
2. The RP-HPLC method was not adequately validated and acceptance criteria for the assays were not acceptable.
3. The release and stability acceptance criteria for amylase and protease and the stability range for lipase were not supported by the data provided.
4. The expiration dating requested was not supported by the data provided.
5. The qualification program for the reference standard was inadequate.
6. The inspection of the DCI facility identified GMP issues that precluded approval of the submission.

The drug substance issues were evaluated by Dr. Richard Ledwidge in his reviews dated 2/1/2012 and 5/15/2012. The issues were satisfactorily resolved and a summary of the resolution is provided in the **Summary of Quality Assessment** section below.

Dr. Howard Anderson evaluated the sponsor's responses pertaining to the drug product issues. The sponsor provided the requested data and Dr. Anderson concluded that the sponsor satisfactorily addressed all the CR letter issues. I concur with his conclusions. A summary of the resolution is provided in the **Summary of Quality Assessment** section below.

SUMMARY OF QUALITY ASSESSMENT

Resolution of the CR issues: Drug substanceBioburden controls:

(b) (4) conducted an analysis of the manufacturing process and historical microbiological data. This analysis was reviewed by OPS Micro and an evaluation of the in-process microbial count limits was also performed by the OBP primary reviewer.

(b) (4) implemented a series of step to improve microbial control during the manufacturing process:

1. (b) (4) developed quality agreements with the gland suppliers that ensured (b) (4). This procedure can considerably reduce the microbial load in the incoming raw materials.
2. (b) (4) improved cleaning procedures and implemented equipment cleaning after every batch of drug substance manufactured.
3. (b) (4) revised the in-process limits for microbial counts based on the analysis of historical results. (b) (4) introduced four control points at which limits are proposed: (b) (4). At the (b) (4) and (b) (4) stage, microbial counts are set to be at no more than (b) (4). (b) (4) specifications have been reduced to no more than (b) (4).

The OPS micro group, as well as the OBP primary reviewer, found these actions adequate to ensure appropriate bioburden control and I concur with their assessment.

B. cereus enterotoxin:

(b) (4) submitted assay development data generated under contract by (b) (4). The data indicated that the positive results in the ELISA assay used to detect *B. cereus* enterotoxin were false positives. The data supported the conclusion that the test approved to detect enterotoxin in food preparations was not suitable for pancrelipase samples. (b) (4) demonstrated that (b) (4) in pancrelipase samples is rapidly degraded by the proteases present in pancrelipase samples. Based on the above points, and the stricter bioburden control implemented by the drug substance manufacturer the OBP reviewer concluded that (b) (4) has adequately addressed the issue of *B. cereus* enterotoxin, and I concur with the reviewer's evaluation.

Intermediate containers:

During the inspection of the drug substance manufacturer facility, FDA investigators noted that (b) (4) had switched intermediate storage containers from (b) (4) to (b) (4). The manufacturer did not conduct extractable/leachable studies and did not inform the Agency of the change. (b) (4) conducted an extractable/leachable study on the (b) (4) containers, and as a result of this study decided to switch to (b) (4) drums. (b) (4) provided stability data and product quality studies for the (b) (4) container, but failed to address the potential presence of metals leaching into the pancrelipase drug substance. **This issue will be addressed as PMC.**

Additional PMCs relate to viral control of pancrelipase, as described in Dr Anderson's reviews dated 8/27/2009 and 9/2/2009.

Resolution of the CR issues: Drug productProcess validation

The sponsor provided the process validation protocol as well as the validation reports. The data resulting from the execution of the validation protocol indicates that the process is robust and can reproducibly manufacture a product that meets the expected quality standards.

Release and stability acceptance criteria for amylase, protease and lipase

DCI provided release data on 11 lots of drug product and revised the specification for release and stability. The sponsor provided a range for amylase and protease (whereas the previous acceptance criteria only provided for a lower limit). The proposed range, (b) (4) of the label claim, is adequate. The sponsor also (b) (4) the stability acceptance criterion for lipase activity to (b) (4) of the label claim. The proposal is acceptable. All proposed specifications are provided in the Appendix of Dr. Anderson's review. Given that the sponsor based the specification on a limited number lots, acceptance criteria for enzyme activity as well as other release assays could be refined further once additional data is available.

This issue will be addressed as PMC.

Dating period and stability protocols

The sponsor provided stability data on lots of drug product under real time, real temperature and accelerated and stressed stability conditions. The data set included data for up to 24 months at real time for both drug product strengths, packaged in 100 and 250 capsules/bottle. The data supported an expiry of 24 month for both strengths in the 100 and 250 capsules/bottle configurations. (b) (4)

DCI incorporated accelerated conditions in the annual stability program (40°C/75%RH) and committed to trend the data and investigate out-of-trend stability results.

The sponsor did not evaluate the stability of drug product manufactured with drug substance at the end of the shelf-life, to evaluate the cumulative stability profile of the drug product. We proposed a protocol where the sponsor will place on stability the first lot of drug product manufactured using drug substance aged beyond drug product manufacturing experience. **This issue will be addressed as a PMC.**

In previous submissions, the sponsor provided stability data, collected over a period of 30 to 60 days, where the bottles were opened 5 times/day at the established conditions (25°C/60% RH or 40°C/75% RH). The data support stability of the product for up to 60 days at the 25°C/60% RH condition and up to 30 days at the 40°C/75% RH condition.

Reference standard qualification

The sponsor proposed a revised qualification program for the reference standard. The revisions included (b) (4) acceptance criteria, running the tests in (b) (4) and establishing assay precision. Furthermore, the RP-HPLC assay has also been included in the

qualification protocol. The proposed protocol is adequate for qualification of a new reference standard.

The sponsor does not have a primary reference standard against which working standard will be calibrated, to avoid drift of the product quality characteristics over time. **This issue will be addressed as PMC.**

RP-HPLC assay

The issues with the RP-HPLC assay pertained to assay validation, acceptance criteria for the assay and system suitability and standard operating procedures.

Regarding validation, the sponsor did not evaluate the protein recovery from the column or data supporting the reuse of the chromatography column. The sponsor provided data indicating that about (b) (4) of the product is recovered from the column. The sponsor provided limited data for column reuse that are sufficient at this time, but did not have an expiration dating for the RP-HPLC column. **This issue will be addressed as PMC.**

Regarding the acceptance criteria for the RP-HPLC peaks, the sponsor (b) (4) the acceptance criteria for individual peaks and peak groups. The proposed revisions are acceptable. **As PMC, the sponsor committed to revise the acceptance criteria for all release specifications after 30 lots of drug product are manufactured.**

Regarding the operating procedures, the sponsor included: 1) a description of the procedure used to quantify impurities; 2) the reference standard as part of the system suitability; 3) a time limit for use of reagents prepared to run the assay, based on development and validation data.

The sponsor adequately addressed all issues related to the RP-HPLC assay.

Compliance issues

Digestive Care, Inc was inspected by ORA field investigators in February, 2012. The investigators concluded that Digestive Care satisfactorily addressed the compliance issues and recommended approval of the application.

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/s/

EMANUELA LACANA
05/16/2012

AMY S ROSENBERG
05/16/2012

Grewal, Jagjit

From: ees_admin@fda.gov
Sent: Thursday, March 08, 2012 1:01 PM
To: Olagbaju, Bose*; Lacana, Emanuela; Anderson, Howard A; Grewal, Jagjit; Salganik, Maria*; Bernstein, Ralph; Biswas, Sumita *
Subject: Overall OC Recommendation NDA 22175/000 Decision: ACCEPTABLE, Decision Date: 03/08/2012, Re-evaluation Date: 06/16/2013

This is a system generated email message to notify you that the Overall Compliance Recommendation has been made for the above Application.

For general questions about how to use EES in your work, send an email to EESQUESTIONS (EESQUESTIONS@cderr.fda.gov). To contact the EES technical staff, send an email to CDER EES Help (EESHHELP@fda.hhs.gov). Thank you.

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

/s/

MARY GRACE LUBAO
05/24/2012



March 8, 2012

NDA: 22-175
PRODUCT NAME: Pertzyme

E LINK: [\\CDSESUB4\NONECTD\NDA022175\4970568](#)
E LINK-PREVOUS SUBMISSIONS: [\\Fdswa150\nonectd\N22175\N_000](#)
E LINK-SPONSPR IR Responses: [\\cdsesub4\NONECTD\NDA022175\5021582 & 5050118 & 5055821](#)

SUBMISSION DATE: November 18, 2011
PRIMARY REVIEW DUE DATE: April 20, 2012
PDUFA GOAL DATE: May 18, 2012

FROM: Howard Anderson, PhD, Biologist
THROUGH: Emanuela Lacana, PhD, Associate Chief Laboratory of Chemistry.

SUBJECT: Product Quality Review of NDA 22-175, Sponsor's Response to FDA Complete Response (CR) Letter, August 27, 2009

SPONSOR: Digestive Care Incorporated (DCI)
PRODUCT: Pancreatic Enzyme Product (PEP) Delayed-Release Capsules 8,000 and 16,000 USP Lipase Units

DRUG SUBSTANCE MANUFACTURER: (b) (4)
(DMF (b) (4))

INDICATION: Exocrine Pancreatic Insufficiency for Cystic Fibrosis (b) (4)

ROUTE OF ADMIN: Oral

CLINICAL DIVISION: Division of Gastroenterology Products and Inborn Errors
RPM: Jagjit Grewal

RECOMMENDATION: **I recommend approval of this application for the drug product perspective. The Pertzyme quality standard is equivalent to current FDA approved PEP products. There are some unresolved product quality issues, but these issues do not preclude approval of the application and can be addressed as post marketing commitments (see below).**

Post Marketing Commitments (To be finalized in Secondary Review)

Drug Substance (b) (4)

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

Final Report Submission by
2. Develop and validate an infectivity assay for PCV1 (Porcine Circovirus 1).

Final Report Submission by
3. Establish lot release specifications for PPV (Porcine Parvovirus) and PCV2 (Porcine Circovirus 2) for the drug substance.

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

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

Final Report Submission by
6. Assess the risk to product quality associated with hokovirus, and submit a control strategy for mitigating the risk to product quality.

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

Final Report Submission by

- 8 Provide the results of leachable/extractable studies for the intermediate storage containers, a risk assessment evaluation and a proposed strategy to mitigate the risk to product quality.
- Final Report Submission by
- 9 Revise release specifications after XXX lots of drug substance 1206 and 1208 lots have been manufactured.
- Final Report Submission by

Drug Product (Digestive Care Inc.)

- 10 Revise release and stability specifications after 30 lots of drug product have been manufactured.
- Final Report Submission by
- 11 Submit a stability protocol used to evaluate and extend the maximum cumulative storage time of the drug substance and drug product. The protocol will provide for placing on stability the first lot of drug product manufactured using drug substance aged beyond drug product manufacturing experience.
- Final Protocol Submission by
12. Establish an expiration date for the RP-HPLC column.
- Final Report Submission by
13. Establish a primary reference standard against which future reference standards will be qualified.
- Final Report Submission by

SUMMARY

This NDA was originally submitted on October 27, 2008. The application was submitted to support the production and marketing of Pertyzme pancrelipase enteric coated Micro Sphere, MS-8, and MS-16 lipase drug products. A summary of the manufacturing process and formulation is provided in the appendix of this review. The proposed release and stability specifications are also provided in the appendix. Dr. Wei Guo, of the Division of Therapeutic Proteins reviewed the original submission. Dr. Guo reviewed DMF [REDACTED] ^{(b) (4)} which supported manufacture of the pancrelipase drug substance. Multiple product quality deficiencies were noted in the original NDA and the drug substance DMF. The deficiencies were communicated to the sponsor, as well as to the DMF holder in FDA Complete Response (CR) letters dated

August 27, 2009.

DCI responded to the FDA CR letter on February 15, 2010. The response was deemed incomplete since it lacked important product quality information. The sponsor provided the information in multiple submissions and the July 27, 2010, submission started the six month PDUFA review cycle. Dr. Howard Anderson and Dr. Emanuela Lacana of the Division of Therapeutic Proteins conducted the primary review. It should be noted that the review of the dissolution items was conducted by ONDQA, and is covered in a separate review. For the Feb. 2010 submission, Dr. Anderson reviewed all drug product CR items except those concerning the RP-HPLC identity and purity assay. Those items were reviewed by Dr. Lacana and were incorporated into the review. Dr. Guo reviewed all items associated with the (b) (4) DMF (b) (4) CR and the information is provided in a separate review. The Feb 2010 submission had improved product quality, however deficiencies still existed and the application was not approved. The FDA sent a complete response letter to DCI dated January 27, 2011.

On November 18, 2011, DCI submitted a response to the January 27, 2011 CR letter, which is the subject of this review. Provided below is the product quality review. In **bold** font are the FDA CR items communicated to DCI in January 2011. They are followed by a summary of the DCI response. Provided in *italic* font is the FDA evaluation of each response. This Submission has addressed all significant outstanding product quality issues. The remaining product quality issue can be addressed as PMCs. They are underlined throughout the review.

On issue that occurred during this review cycle, was that it was discovered that the label claim for the amylase and protease potencies was determined by (b) (4). An Information Request (IR) was sent to the sponsor indicating that this was inappropriate and not compliant with 21 CFR 201.51(g). The sponsor provided a response on April 6, 2012 and the label was revised and NDA release and stability results were updated to reflect the new revised label claim. The revised potencies are provided in the sponsor table below.

Name of Active Ingredients	Label Claim Unit Quantity (USP Units/ Capsule)	
	MS-8	MS-16
Dosage Strength (DCI Internal Code Designation)		
Pancrelipase, USP	Lipase	8,000
	Amylase	30,250
	Protease	28,750

	Lipase Activity (USP Units/Cap)	Amylase Activity (USP Units/Cap)	Protease Activity (USP Units/Cap)
MS-16 Clinical Lot 6K09B ACTUAL Enzyme Content	(b) (4)		
Rounded for Label Claim designations on Labeling	16,000	60,500	57,500

The appendix of this review contains;

1. Product Unit Composition
2. Product Release and Stability Specifications
3. Clinical Lot Release and Stability Data
4. Batch Analysis of Lots Supporting NDA approval

COMPLETE RESPONSE REVIEW

FDA CR ITEM 1.

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

FDA Comment

(b) (4) DMF (b) (4) has been updated to address all issues that precluded approval of this NDA. DMF (b) (4) supports the manufacture of two FDA approved PEPs (NDA-2222, Ultresa & NDA 22542 Viokace). A review of the information requested, and all product quality issues associated with DMF (b) (4) is located in multiple Division of Therapeutic Protein product quality reviews (see DARRTs). These include;

CMC

Dr. Wei Guo – June 2009, September 2009, April 2010, October 2010, & September 2010

Dr. Richard Ledwidge – February 2012

CMC Viral Issues

Dr. Howard Anderson – August 2009 & September 2009

Dr. Ennan Guan – July 2008

Outstanding issues still exist with the (b) (4) DMF regarding viral issues. They do not preclude my recommendation for approval since they can be addressed as PMCs. They are currently PMC for all the sponsors of PEPs approved by FDA.

FDA CR ITEM 2.

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

DCI Response

DC provided a process validation summary report, PVR-003. The sponsor has conducted process validation on three consecutive lots for both the 8 K & 16 K lipase strengths (Lots - PC 11H06B-16, PC 11H07B-16, P11I08B-16, PC 11H06B-8, PC 11H07B-8, P11I08B-8,). Provided in the table below is a summary of the validation strategy, process operating parameters, and performance parameters/in-process tests. The prospective validation was successful and there were no major deviations.

Summary of the Drug Product Validation Strategy & Validation Reports

Phase	Description of Activity	Validation Protocol/Report	Associated Batch Records and SOPs
(b) (4)			

Validation Operating Parameters and Performance Parameters

VALIDATION PROCESS CONTROL AND QUALITY VARIABLES

(b) (4)



VALIDATION PROCESS CONTROL AND QUALITY VARIABLES

(b) (4)

FDA Comment

DCI has been manufacturing the product since 1990, and all acceptance criteria were largely based on historic manufacturing capability. The process validation was conducted prospectively and the Quality Unit approved protocol was followed. One issue that arose during this review was that in the Nov. 2011, submission the sponsor did not provide the actual process operating parameters and performance parameters for each of the three validation lots. All data were presented as “within specification”. The information was required to evaluate the validation study and was requested by the FDA in February 2012, and provided by DCI. The data was reviewed and found to be adequate. The process performed within all predefined acceptance criteria and there were no major protocol deviation, out of trend, or out of specification events. The validation strategy is very similar to that used by other manufacturers for FDA approved pancreatic enzyme products (PEPs).

In response to the FDA IR request the sponsor provided all batch product records (BPR) for the validation lots. The BPRs provided are summarized in the table below.

Table 4. List of Executed PV Batch Records

Process Phase	Lot PC-11H06B	Lot PC-11H07B	Lot PC-11I08B
(b) (4)			

Process Phase	Lot PC-11H06B	Lot PC-11H07B	Lot PC-11I08B
(b) (4)			

The BPRs were used as a reference to review PVR-003 and were only briefly reviewed. They were reviewed during the preapproval inspection conducted by ORA, and no major deficiencies were noted. The FDA inspector has recommend approval of the DCI facility. (b) (4) 483 items were issued to the company regarding filter issues. Provide below are the results of release testing for the three consecutive validation lots.

Validation Lot Release Testing

Table B. Testing Summary – Finished Product (MS-8)

Test	Specification	Lot PC-11H06B-08	Lot PC-11H07B-08	Lot PC-11I08B-08
(b) (4)				
[Redacted Content]				

Digestive Care, Inc. Confidential Information	ATTACHMENT 2	NDA 22-175 Response to RFI Dated February 17, 2012		
Test	Specification	Lot PC-11H06B-08	Lot PC-11H07B-08	Lot PC-11I08B-08
(b) (4)				
[Redacted Content]				
Microbial Purity				
Fill Weight Uniformity				
Final Testing Summary (Pass/Fail)		Pass	Pass	Pass

The DCI manufacturing process validation can be considered validated. A few points to note are;

1. The sponsor has performed weight checks at the beginning, middle and end of the process to demonstrate content uniformity. The Pertyzme drug product was uniform as defined by USP<905> (within the range of 85% to 115% of specified fill weight). This standard is currently used for approved PEP products.
2. The validation results indicate that there is not difference (b) (4) is conducted at the upper and lower limits of the operating parameters (b) (4)
3. The sponsor also performed a 100% visible fill check. There was not a significant rejection of capsules (b) (4)
4. In the Feb 2011, FDA IR the sponsor was asked to provide a summary of all significant manufacturing changes that have occurred since production of the single M-16 clinical lot (6K09B). Provided below is the sponsor's summary of all changes that have occurred since the clinical material was manufactured. The changes are considered minor and not likely to affect product attributes.

Process Phase	Description of Difference
(b) (4)	

In summary, the DCI manufacturing process operates in a state of control and can be considered validated. The information provided in this submission is adequate and the CR item has been resolved.

FDA CR ITEM 3.

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

- a. **You did not establish an upper limit for the acceptance criteria for the protease and amylase potency assays for release and stability testing. Lack of an upper limit**

would allow for wide excursions of amylase and protease potencies, beyond the results obtained on the clinical trial material and on your historical lots. In order to ensure consistency of the drug product amylase and protease potencies, you should establish and justify release and stability acceptance ranges for amylase and protease.

DCI Response

This item is addressed in item 3.b.ii

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

i. An explanation addressing the fluctuation in lipase activity.

DCI Response

The sponsor states that the increase in lipase activity for lot PC-6H05B is not representative of historic lipase activity observed during stability studies. This lot appears to be an outlier. The reason for the excursion is not know, but DCI has committed to continue evaluating stability results and trending data.

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

DCI Response

The sponsor provided data for release and stability testing of 11 lots. The lipase stability specification has now been (b) (4) activity. For reference, provided in the table below are representative stability for the MS-16 and MS-8 strengths.

FDA Comment

The release and stability data for the 11 lots have been reviewed are adequate to justify the sponsor's new proposed acceptance criteria for the enzyme activities. The sponsor's has (b) (4) the stability lipase potency acceptance range to (b) (4) potency ranges is acceptable at this time considering the limited manufacturing data and precision of the assays. There are also limited clinical data as only one lot was evaluated in the clinic. The sponsor, for a PMC should reevaluate all specification after additional lots are manufactured (e.g. n=30) and the acceptance criteria should be (b) (4) as appropriate. This PMC has been required for the five other FDA approved PEP manufacturers.

FDA CR ITEM 4.

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

DCI Response

The sponsor has provided stability data for 11 lots and the stability lots are provided below. In the Feb sponor’s IR that stability data was updated for lots (9J27B, 9J30B, 9I33B, 9I36B, 9I37B, and 9I38B) since stability data were obtained after the NDA CR submission. Representative data are provided below indicating the product is stable for the proposed two year expiry.

Table (3.2.P.8.1)I. Drug Product Stability Lots			
	Room Temperature (25°C/60%RH) Months (in progress)	Intermediate Temperature (30°C/65%RH) Months (in progress)	Accelerated Temperature (40°C/75%RH) Months
Packaged in 100 capsules/bottle			
MS-8 (8,000 USP units of lipase/capsule)			
PC-9A01B	(b) (4)		
PC-9J27B	(b) (4)		
PC-9J30B	(b) (4)		
MS-16 (16,000 USP units of lipase/capsule)			
PC-6H05B	(b) (4)		
PC-6K09B	(b) (4)		
PC-7A01B	(b) (4)		
PC-8H16B	(b) (4)		
PC-9L38B	(b) (4)		
Packaged in 250 capsules/bottle			
MS-8 (8,000 USP units of lipase/capsule)			
PC-9L33B	(b) (4)		
MS-16 (16,000 USP units of lipase/capsule)			
PC-9L36B	(b) (4)		
PC-9L37B	(b) (4)		





FDA Comment

DCI is proposing a two year expiry for the MS-16 and MS-8 beads when stored at 25°C/60% RH. The stability lots are provided in the sponsor's table below above. All stability data have been reviewed and supports the proposed two year expiry. The two product strengths are to-be-marketed in either 100 capsules/bottle, 250 capsules/bottle

(b)
(4)



(b) (4)

- 1) *Real time data was provided for the MS-16 packaged in 250 capsules/ bottle (PC-9L36B & PC-9L37B) or in 100 capsules/bottle (PC-9L38B) and the product remains stable for at least 24 months (25oC/60%RH). Slight increases in product related impurities in the RP-HPLC assay were observed. However, they are not considered significant. These differences during storage of the product occur with other FDA approved PEPs. Adequate real-time stability data have been provided to support the two year expiry of the MS-16 product.*
- 2) *Real time data was provided for the MS-8 lots packaged in the 250 capsules/bottle (PC-9L33B) or in the 100 capsules/bottle ((PC-9J27B & PC-9J30B) was provided. There was a slight (b) (4) trends (b) (4) of potency for some historic lots for enzyme activities, and dissolution assay results for the MS-8 lots. The trend was not seen in all lots. This trend was more evident when the product was analyzed at accelerated conditions (30°C/65%RH). The product remained well within specification. The slight decrease in potency in some of the lots is not considered to have an impact on the products clinical performance. This same trend (b) (4) was observed with other FDA approved PEP products.*
- 3) *The product does show breakdown when stored at accelerated conditions (ICH) supporting the stability indicating potential of the assays.*

Overall the sponsor has provided adequate data to support the MS-8 and MS-16 expiry for the 100 and 250 capsule/bottle. As stated above the sponsor should commit to reevaluate the acceptance criteria for all assays and adjust appropriately when additional manufacturing experience is gained with this product.

FDA CR ITEM 5.

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

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

- a. Your acceptance criteria should be (b) (4) the release acceptance criteria and should be based on your historical trend results as well as on the results of testing conducted on the clinical trial material.
- b. Establish upper limits for the protease and amylase specifications.
- c. Incorporate the RP-HPLC assay in your reference standard qualification protocol.

DCI Response

The Internal Drug Product Reference Standard (IDPRS) qualification program has been updated. The acceptance criteria for the enzyme activity testing have been increase and the test will be run in (b) (4). Acceptance criteria have now been established for assay precision. The updated qualification program is provided in the tables below. The IRBS will be stored at 5°C and assigned a (b) (4) expiry.

Table (3.2.P.6)2. Use of the IDPRS during Release and Stability Testing

TEST	TEST METHOD	ACCEPTANCE CRITERIA FOR THE IDPRS
Lipase Activity	TM-6013	(b) (4)
Amylase Activity	TM-6012	
Protease Activity	TM-6014	
Dissolution Lipase Activity	TM-6007	
SDS-PAGE	TM-6069	
RP-HPLC	TM-6083	

Table (3.2.P.6)1. IDPRS Qualification Specification

TEST	TEST METHOD	ACCEPTANCE CRITERIA
Lipase Activity	TM-6013	%RSD of lipase specific activity NMT (b) (4)
Amylase Activity	TM-6012	%RSD of amylase specific activity NMT (b) (4)

Protease Activity	TM-6014	%RSD of protease specific activity NMT (b) (4)
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NMT = Not More Than; RSD = Relative Standard Deviation

FDA Comment

The sponsor's has improved the reference standard (RS) qualification program and has addressed this CR item to support licensure. Upper limits have been established for all specifications, acceptance criteria have been updated and are (b) (4) those used for product release, and a RP-HPLC method is now being used. The acceptance criteria are in line with the clinical trial lot (MS-16 6K09B, see appendix). One issue that is still outstanding is that the RS qualification program does not include the establishment of a primary reference standard. The primary standard should be stored under conditions in which it is most stable and used for the qualification of future reference standards. This issue will be addressed as a PMC.

FDA CR ITEM 6.

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

DCI Response

The sponsor has agreed to modify the stability program to include the evaluation at ICH accelerated conditions (40°C/75%RH). DCI commits to trend the data to historical results and evaluate excursions. The stability program is provided below. The appendix of this review contains the stability evaluation specifications.

Table (3.2.P.8.2)1. Post Approval Annual Stability Program Protocol

Storage Condition	Time (Months)						
	Initial: Full Product Release Testing	3	6	9	12	18	24
25°C/60%RH			X		X	X	X, M
40°C/75%RH		X	X				
X = Visual Appearance, (b) (4) Enzyme Activity Assays (lipase, amylase, protease), Dissolution, RP-HPLC							
M = Microbial Purity							

FDA Comment

The sponsor has updated the annual stability program as requested by the FDA to include an evaluation of the product when stored at accelerated conditions. This CR item has therefore been adequately addressed.

FDA CR ITEM 7.

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

DCI Response

The sponsor states that method was validated at (b) (4) and transferred to DCI. The method was implemented at DCI in May 2011 (TM-6083). Specifications are provided below.

Table (3.2.P.5.6)3. RP-HPLC Proposed Acceptance Criteria (Release and Stability) (b) (4)



a. You have provided acceptance criteria for six enzyme peaks and for several impurities. However, you have not established acceptance criteria for the appearance of new peaks or for minor peaks that are not included in your acceptance criteria. Lack of monitoring for new impurities or minor peaks would

allow for changes in the purity/impurity profile of your product. You should update your acceptance criteria appropriately.

DCI Response

A specification has been established (see the table above).

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

DCI Response

The sponsor has analyzed 19 lots of samples stored at 25°C for 30 months. Specifications are supporting are provided above. The RP-HPLC data are summarized in the sponsor's table below.

Table (3.2.P.5.6)4. Summary of Available RP-HPLC Data for MS-16 and MS-8 Lots (stored at 25°C) from 0-30 Months

(b) (4)

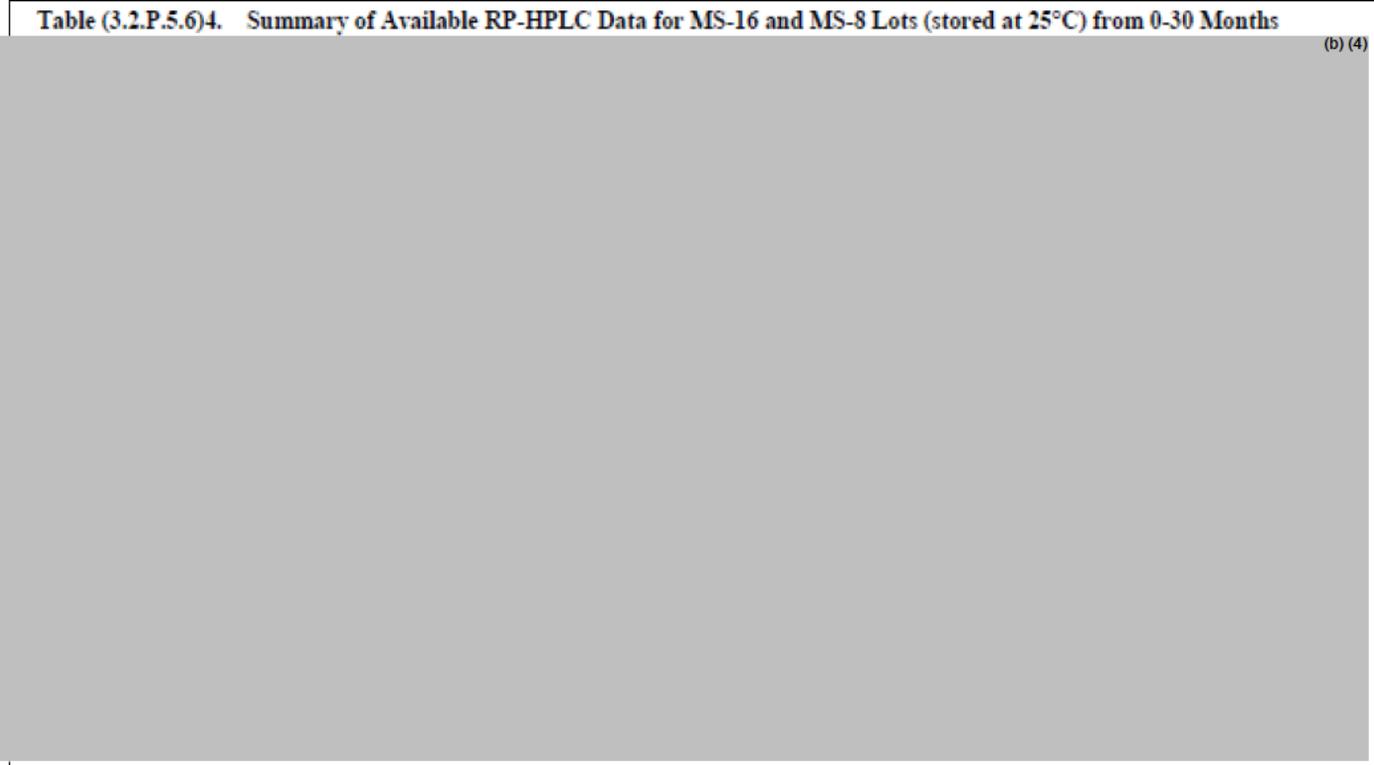


Table (3.2.P.5.6)5. Summary of Available RP-HPLC Data for MS-16 and MS-8 Lots (stored at 25°C) from 0-30 Months

(b) (4)

FDA Comment

The sponsor has provided the requested data to support the test methods acceptance criteria. The acceptance criteria are approximately (b) (4). This method was not performed to evaluate the clinical lot. For approval the acceptance criteria is appropriate and will be reevaluated and adjust as more manufacturing experience is gained with the product (See below).

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

DCI Response

The sponsor has provided Report RR-234 and indicates that (b) (4) of the protein sample is recovered for the column. The remaining (b) (4) from the column with the (b) (4). The sponsor performs a system suitability check every time the assay is performed. A column life time has not yet been established and will be when it is determined the duration of time at which a column fails the suitability check.

FDA Comment

The sponsors report has been reviewed and it adequately describes the study to evaluate drug product retention on the column. The sponsor has provided the requested information to support approval of this application. The sponsor should commit to the PMC to establish a column expiry.

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

FDA Comment

The sponsor has provided the method SOP (TM-6803). The information adequately addresses this CR method. It should be noted that the method transfer was evaluated in the FDA product review from January 2011, and found to be adequate.

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

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

FDA Comment

DCI has now updated TM-6803 to include the use of a drug product reference standard (see page 4 of the SOP). This CR item has been adequately addressed.

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

FDA Comment

The sponsor has updated TM-6903 (page 10) to include of description of how impurities are quantified. The calculation (linear regression) has been reviewed and it is appropriate. This item has therefore has been appropriately addressed.

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

FDA Comment

TM-6903 has been updated (see page 6) to specify that test samples are to be evaluated (b) (4) of reagent preparation. The test method has been updated as requested by the FDA. This CR has therefore been adequately addressed.

Overall the sponsor has provided the appropriate information and updated the RP-HPLC test method. It should be noted that DCI has committed to reevaluate the RP-HPLC assay acceptance criteria for the individual peaks after 25 lots are analyzed. Reevaluating all product release and stability specifications will be addressed as a PMC (see IR #3).

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/s/

HOWARD A ANDERSON
04/17/2012

EMANUELA LACANA
04/17/2012

December 17, 2010

NDA: 22-175
PRODUCT NAME: Pertzyme

SUBMISSION DATE: 2/17/2010, 3/24 & 25/2010 (Dissolution Method),
7/29/2010 (RP-HPLC Method)
PDUFA GOAL DATE: 1/29/2011

FROM: Howard Anderson, PhD, Biologist
THROUGH: Emanuela Lacana, PhD, Associate Chief Laboratory of Chemistry.

SUBJECT: Amendment to Clarify CR Item 2c
(Product Quality Review of NDA 22-175 Drug Product FDA
Complete Response Letter August 27, 2009)

PRODUCT: Pancreatic Enzyme Product (PEP)
Delayed-Release Capsules

INDICATION: Exocrine Pancreatic Insufficiency for Cystic Fibrosis (b) (4)
[REDACTED]

ROUTE OF ADMIN: Oral

SPONSOR: Digestive Care Incorporated

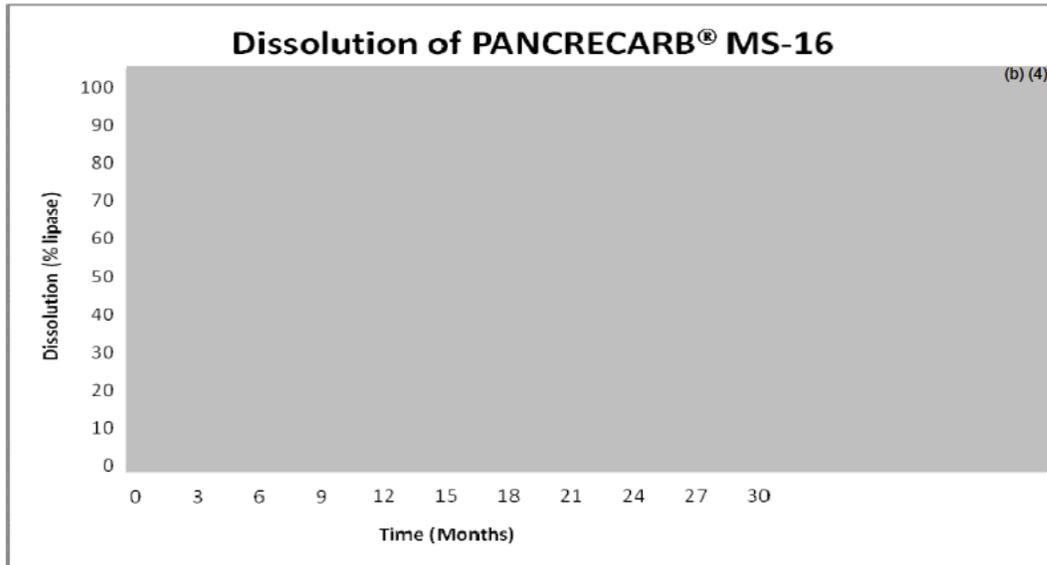
CLINICAL DIVISION: Division of Gastroenterology Products
RPM: Matthew Scherer

This amendment is to indicate that CR item 2C regarding the dissolution testing on the product was reviewed. The updated data indicate that there is no (b) (4) trending of the dissolution data for three lots of MS-16, and one lot of (b) (4) MS-8 drug products suggesting that this product quality attribute is stable over the 30 month time period of storage. Issues however, still exist since the testing methodology appears to be deficient (as per dissolution review conducted by ONDQA). The sponsor states in the 2010-02-17 submission (item 1C) that, "DCI agrees to implement an acceptance limit of (b) (4) (Q) for dissolution for release and stability of the drug product. The revised Drug Product Stability Specifications are shown in Table 02 (3.2.P.8).

Table 02 (3.2.P.8) Drug Product Stability Tests and Specifications

Test	Method	Drug Product Stability Specifications
(b) (4)		

Dissolution testing is done using test method TM-6007 (Table 02 (3.2.P.8) above). The dissolution values (% lipase) at release and on stability appear to be (b) (4) and are provided in the figure below. The dissolution assay methodology is being reviewed by ONDQA (for CR item 1C), and deficiencies still exist with the assay. Thus stability data will be re-evaluated when the deficiencies identified by the ONDQA reviewer have been addressed.



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/s/

HOWARD A ANDERSON
01/25/2011

EMANUELA LACANA
01/25/2011

**December 17, 2010****NDA:** 22-175
PRODUCT NAME: Pertzyme**SUBMISSION DATE:** 2/17/2010, 3/24 & 25/2010 (Dissolution Method),
7/29/2010 (RP-HPLC Method)
PDUFA GOAL DATE: 1/29/2011**FROM:** Howard Anderson, PhD, Biologist
THROUGH: Emanuela Lacana, PhD, Associate Chief Laboratory of Chemistry.**SUBJECT:** Product Quality Review of NDA 22-175 Drug Product FDA
Complete Response Letter August 27, 2009**PRODUCT:** Pancreatic Enzyme Product (PEP)
Delayed-Release Capsules**INDICATION:** Exocrine Pancreatic Insufficiency for Cystic Fibrosis (b) (4)
[REDACTED]**ROUTE OF ADMIN:** Oral**SPONSOR:** Digestive Care Incorporated**CLINICAL DIVISION:** Division of Gastroenterology Products
RPM: Matthew Scherer**RECOMMENDATION:** **I do not recommend approval of this application since deficiencies still exist that could significantly impact the quality of Pertzye drug product. Deficiencies that need to be addressed include; a lack of process validation, a RP-HPLC QC assay, an inappropriate acceptance criteria for protease and amylase potencies, an inadequate reference standard qualification program, and a lack of real time stability data to support the (b) (4) MS-8 expiries.**

Draft Product Quality Complete Response Items to be Communicated to DCI (Final Version in Secondary Review)

- 1) You have not provided prospectively validated the Pertzyme Drug Product manufacturing process. Please provide prospective process validation reports with all relevant supporting data to demonstrate that your process is adequately controlled.
- 2) The acceptance criteria for the protease and amylase potency assays for release and stability testing, as well as qualification of new reference standards does not contain an upper limit. Please establish and just an upper limit for the specifications.
- 3) The acceptance criteria range for lipase stability is (b) (4) activity, which is significantly different from acceptance criteria (b) (4) specified for lot release. The (b) (4) acceptance criteria are not adequately justified by the data provided in the application. Please comment on the following;
 - a. Lot PC-6K09B is significantly different for the two other lots used to support the acceptance criteria. Additional lots may need to be analyzed to establish an accurate acceptance criteria for lipase activity during storage of the MS-16 drug product.
 - b. Lipase activity appears to increase during storage of the MS-16 drug product. No information has been provided in the application to address the apparent wide fluctuations in lipase activity during storage of the MS-16 drug product.
- 4) A (b) (4) expiry is requested for the (b) (4) MS-8 drug products. Nine months of real-time stability data are provided in the application. Please provide real-time stability to support all expiries.
- 5) The RP-HPLC assay to be performed for release and stability testing of Pertzyme is not adequate. Please address or provide information for the following items;
 - a. The assay SOP for the method conducted at (b) (4) and DCI.
 - b. The assay procedure should include the analysis of a reference standard.
 - c. The procedure used to quantify impurity levels.
 - d. Data to support the stability of test samples for up to (b) (4) (only two days of stability data have been provided).
 - e. Acceptance criteria should be established and justified for all individual peaks. An acceptance criteria should be established to exclude the appearance of any new peak.
 - f. The acceptance criteria on stability are (b) (4) at 30 months than the criteria at release. This suggests the product may not be stable after 30 months of storage. Acceptance criteria at the proposed

two year expiry need to be established and justified. Product should remain stable for the proposed expiry.

- g. The acceptance criteria for many of the peaks may not be appropriate. The acceptance criteria are (b) (4) and appear to not account for the variability associated with the assay precision or the manufacturing process.
- 6) DCI proposes to implement a RP-HPLC program as part to the release and stability program as well as the reference standard qualification program. The assay should be implemented prior to the approval of this NDA. It is not clear from the current submission that the assay has been implemented.

Summary

This NDA was originally submitted on October 27, 2008. The application is to support the production and marketing of Pertyzme pancrelipase enteric coated Micro Sphere (b) (4), MS-8, and MS-16 lipase drug products. Dr. Wei Guo of the Division of Therapeutic Proteins reviewed the original submission. Dr. Guo reviewed DMF (b) (4) (b) (4) which supported manufacture of the pancrelipase drug substance. Multiple product quality deficiencies were noted in the original NDA and the DMF. The deficiencies were communicated to the sponsor, as well as to the DMF holder in FDA Complete Response (CR) letters on August 27, 2009.

This complete response (CR) was originally submitted to FDA on February 15, 2010. It however was deemed incomplete since it lacked important product quality information. The information was provided in multiple submissions by DCI on July 27, 2010, submission started the six month PDUFA review cycle. Dr. Howard Anderson and Dr. Emanuela Lacana of the Division of Therapeutic Proteins conducted the primary review. It should be noted that the review of the dissolution items (items 1c & 2c) was conducted by ONDQA, and is covered in a separate review. For this review Dr. Anderson reviewed all drug product CR items except those concerning the RP-HPLC identity and purity assay (items 1a & 2a). Those items were reviewed by Dr. Lacana and are incorporated into this review. Dr. Lacana reviewed all items associated with the (b) (4) (b) (4) DMF (b) (4) CR and the information is provided in a separate document.

Digestive Care Incorporated (DCI) has made significant improvements in the application in this CR response. However major deficiencies need to be addressed before I can recommend approval of the application. The deficiencies that still need to be addressed include;

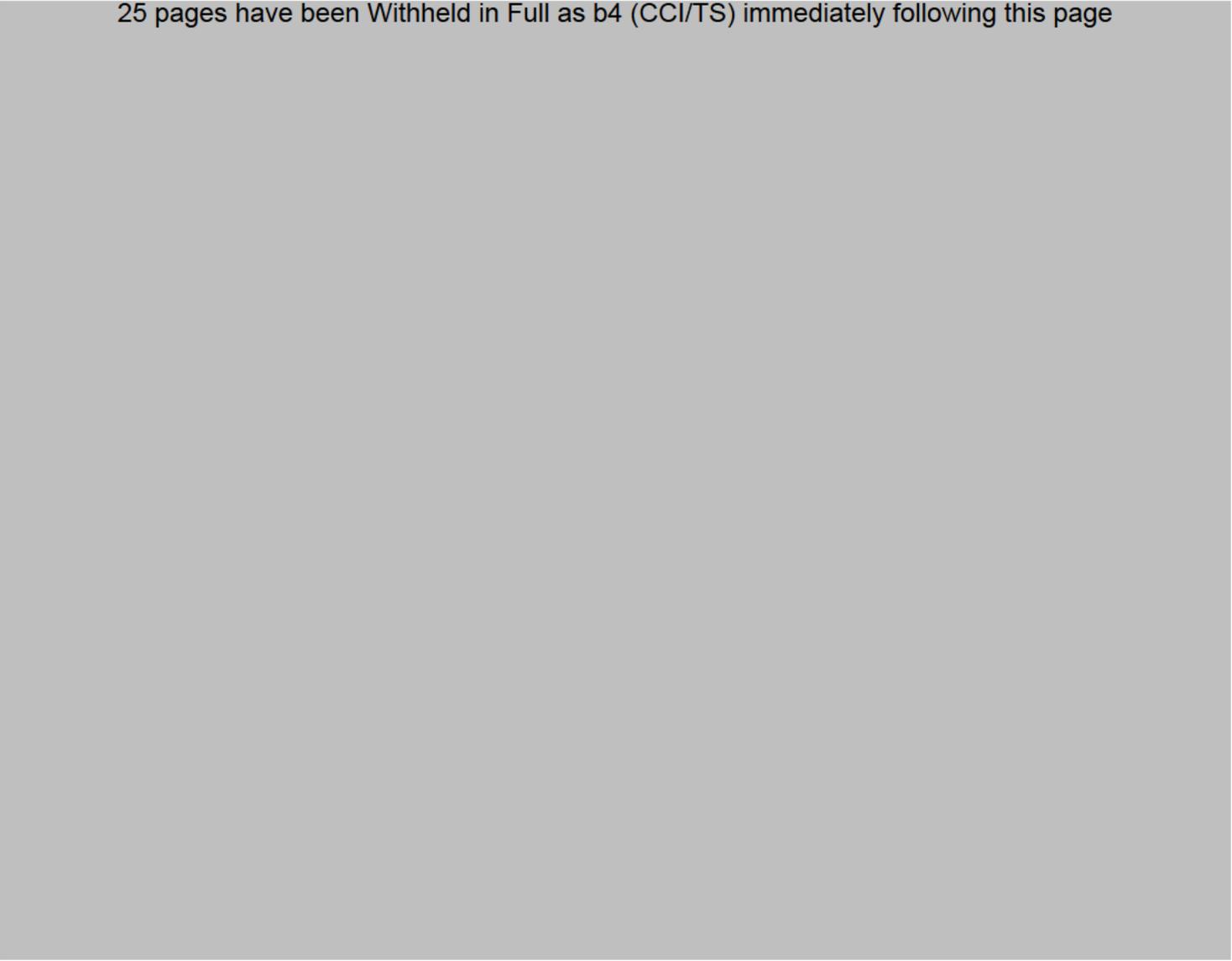
1. The manufacturing process has not been prospectively validated.
2. The acceptance criteria for the protease and amylase potency assays used for release, stability testing and qualification of the reference standard does not specify an upper limit.
3. The lipase stability acceptance criteria of (b) (4) is not adequately justified.
4. Real-time stability data are not provided to support the proposed (b) (4) expiry of the (b) (4) MS-8 drug product strengths.

5. A validated RP-HPLC assay has not been fully developed. It should be implemented to monitor for identity, product related impurities for product release and stability evaluation. The RP-HPLC method should also be included in the qualification of new reference standards.
6. There are still outstanding issues with DMF (b)(4) that will be covered in a separate review.

Provided below is the product quality review. In **bold** font are the CR items communicated to DCI in August 2009. They are followed by a summary of the DCI response. Provided in *italic* font is the FDA evaluation of each response. It should be noted that deficiencies that are to be communicated to the sponsor are underlined throughout the review.

Complete Response Review

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/s/

HOWARD A ANDERSON
01/20/2011

EMANUELA LACANA
01/20/2011

Team Leader Memo NDA22175 Pancrelipase (PERTZYE)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Center for Drugs Evaluation and Research – Food and Drug Administration
Office of Biotechnology Products / Office of Pharmaceutical Science
Division of Therapeutic Proteins

Team Leader Memo NDA 22175

From: **Emanuela Lacana, Ph. D**
Division of Therapeutic proteins (DTP)

Through: **Barry Cherney, PhD**
DTP Deputy Division Director

NDA Number: **022175**
Product: **Pancrelipase (PERTZYE)**
Sponsor: **Digestive care, Inc,**

Date of Review: **December 30, 2010**

SUMMARY OF QUALITY ASSESSMENT

Recommendation and conclusions on approvability:

The Division of Therapeutic Proteins does not recommend approval of NDA22175. The sponsor has not satisfactorily addressed some of the issues that were communicated in the CR letter issued on August 27, 2009. Specifically:

1. The sponsor did not provide prospective process validation protocol and reports.
2. The RP-HPLC assay acceptance criteria and method are inadequate.
3. The release and stability acceptance criteria for amylase and protease, and the stability acceptance range for lipase are not justified and are not supported by data.
4. The qualification program for the reference standard is inadequate.
5. The requested expiration date for the (b) (4) 8000U strength is not supported by the data provided.
6. Several GMP deficiencies were identified during the inspection of Digestive Care, Inc. As of 1/20/2011, there is a withhold recommendation from the Office of Compliance regarding the GMP status of DCI.

Additionally, there are pending issues with the drug substance manufacture that need to be resolved prior to approval of NDA22175:

1. During inspection of (b) (4), inspectors noted that changes to the drug substance intermediate container were introduced into the process, and the DMF holder was cited for lack of extractable leachable data. The DMF holder had not reported the change to the Agency or to the NDA holder. The Agency requested the change to be reported. However (b) (4) did not provide validation data or extractable/leachable studies for the new container. This issue was discovered after the primary review was completed and for this reason is not discussed in Wei Guo's review.
2. Both FDA field laboratories and CFSAN laboratories have analyzed samples of pancrelipase from (b) (4) for the presence of *Bacillus cereus* diarrheal enterotoxin and detected the toxin in several samples. (b) (4) claims that the positive results are false positives and are due to matrix interference. However, the DMF holder has provided no data to support this contention.
3. (b) (4)

Complete Response Letter Comments:

1. You have provided retrospective validation reports for the Pertzye Drug Product manufacturing process. The retrospective validation does not take into account manufacturing development and manufacturing changes and changes in analytical testing techniques. Since 2004, you have introduced changes in the manufacturing process of the MS16 strength and changes in analytical testing. Furthermore, no validation data was submitted for the new (b) (4) MS8 strengths. Given these issues and the complexity of protein products, a prospective process validation should be conducted, to demonstrate your ability to consistently manufacture a product that meet the expected quality standard. Please provide prospective process validation reports with all relevant supporting data for the (b) (4) MS8 and MS16 strengths, to demonstrate that your process is adequately controlled.
2. In regard to your release and stability acceptance criteria, we have the following comments:
 - a. You did not establish an upper limit for the acceptance criteria for the protease and amylase potency assays for release and stability testing. Lack of an upper limit would allow for wide excursions of amylase and protease potency, beyond the results obtained on the clinical trial material and on your historical lots. In order to ensure consistency of the drug product amylase and protease potency, please establish and justify release and stability acceptance ranges for amylase and protease.
 - b. You have established a lipase stability acceptance range of (b) (4) activity, which is significantly different from the acceptance range (b) (4) you have established for lot release. The (b) (4) acceptance range is not adequately justified by the data provided in the application and it is unclear how the proposed limits relate to your clinical experience. The lipase activity result you have obtained for lot PC-6H05B is significantly different (b) (4) than lots PC-6K09B and PC-7A01B. Furthermore, from the data you have provided, it appears that lipase activity shows a transient increase during storage of the MS-16 drug product. Please provide:
 - i. An explanation addressing the fluctuation in lipase activity.
 - ii. Additional justification for the proposed limits with supporting data, or a revision of the lipase stability acceptance criterion, as appropriate.
3. You are requesting a (b) (4) expiry for the (b) (4) MS-8 drug products. However, you have submitted only nine months of real-time stability data in the application. Expiration dating of protein products is based on real-time, real temperature stability data. Please provide real-time stability data that support your requested expiry dating or revise the dating period.

4. You are proposing a qualification program for your drug substance reference standard that includes release testing assays. The acceptance criteria you have established for the qualification program are the same acceptance criteria you are using for release testing. Use of the release acceptance criteria could potentially allow for product characteristics in the new reference standard to be out of trend with the desired or expected product characteristics, thereby introducing drift into the product over time. Please update your reference standard qualification program, as follows:
 - a. Your acceptance criteria should be (b) (4) the release acceptance criteria and should be based on your historical trend results as well as on the results of testing conducted on the clinical trial material.
 - b. Establish upper limits for the protease and amylase specifications.
 - c. Incorporate the RP-HPLC assay in your reference standard qualification protocol.
5. Your annual stability program for drug product provides for one lot of material to be entered in the stability program at the proposed storage conditions. However, the purpose of the annual stability program is not to confirm stability at the intended storage conditions, but rather to demonstrate that routine changes such as rotation of operators or minor equipment changes do not have a significant impact on the stability profile of the product. Stability studies conducted under the recommended storage conditions may not be not adequate to address this issue because little or no degradation is likely to occur under these conditions even when there is a problem with product stability. Please incorporate accelerated and/or stressed stability studies in your annual stability program for drug product.
6. You have provided development and validation studies in support of a new RP-HPLC assay to be performed for release and stability testing of Pertzye. However, it is not clear whether the assay has been implemented. Please provide available release and stability data that include the RP-HPLC assay. Furthermore, please address or provide information for the following items:
 - a. You have provided acceptance criteria for six enzyme peaks and for several impurities. However, you have not established acceptance criteria for the appearance of new peaks or for minor peaks that are not included in your acceptance criteria. Lack of monitoring for new impurities or minor peaks would allow for changes in the purity/impurity profile of your product. Please update your acceptance criteria appropriately.
 - b. You have established stability acceptance criteria based on the results obtained on two 30-month old lots. These acceptance criteria would allow for significant decreases in enzyme content, and are not adequately justified. Please provide a justification with supporting data for your stability acceptance criteria for RP-HPLC or revise as appropriate.

- c. In your validation studies you have not evaluated % recovery of the protein samples after chromatography. Protein retention on the chromatography column could provide inaccurate assay results. Additionally, there are no studies that evaluate the lifetime and performance of the chromatography column. Use of the column at the end of the lifetime might result in inadequate protein sample separation and altered elution profiles that would provide inaccurate assay results. Please provide information on sample recovery and validation studies supporting column performance and reuse.
- d. You have provided the method description for the RP-HPLC assay conducted at (b) (4). However, you have not submitted the method description for the assay conducted at DCI. Since DCI is the site at which the RP-HPLC assay used for release and stability testing will be conducted, please provide the DCI method description and Standard Operating Procedure. (SOP). In regard to the (b) (4) method, we have the following comments:
- i. You are using a purified elastase standard curve to determine the quantity of the enzymes you have selected to report. However, you have not included a drug product reference standard, to be run along the samples. The reference standard will ensure that the chromatographic profile of the sample is consistent and that no new peaks appear. Please include a reference standard to be run in each assay.
 - ii. You provided information on how to calculate quantities of the enzymes you have selected to report. However, there is no description of how the impurities levels should be quantified. Without this information, the peak impurity levels cannot be evaluated. Please update your method to include a description of the procedures used to quantify impurities levels.
 - iii. In your method, you state that samples and (b) (4) are stable for (b) (4). However, the study you have conducted to evaluate sample stability was carried out for two days, and no study was conducted to evaluate the stability of the solvents. The data you have submitted does not support stability of the sample or (b) (4) for the period of time indicated in the method. Therefore, please provide the results of studies that demonstrate that samples and (b) (4) are stable for (b) (4), or revise your method based on your current supporting data.

Summary of Chemistry Assessments:

A complete summary assessment of product quality is covered in the Team Leader memo associated with the review of the original application. A number of issues were identified during the review cycle that precluded approval of the application. DCI was issued a Complete Response letter on August 27, 2009. This summary will cover exclusively the sponsor's response to the CR letter.

One of the major issues identified during the previous review cycle was the absence of an assay to monitor product purity and impurities at release and during stability. The sponsor developed and provided validation studies for a Reverse-Phase HPLC assay, to be used for release and stability testing. This is a standard assays used by both drug substance and drug product manufacturers of PEPs to monitor purity and impurities.

The development and validation studies presented by the sponsor overall demonstrated that the assay is robust, precise, reproducible and identify specific enzymes in the chromatogram. The sponsor conducted forced degradation studies, where pancrelipase was subjected to stress condition (acid, base, temperature) and then analyzed by RP-HPLC. The sponsor demonstrated that the assay is suitable to monitor product degradation. However, issues still remain unresolved with the assay:

1. The sponsor proposed acceptance criteria for six enzymes (b) (4) and for additional peaks identified by Relative Retention Time (RRT), based on an external purified elastase standard. While this method can provide semi-quantitative information, pancrelipase is a complex product and the chromatogram resolves multiple peaks. The sample should also be analyzed against a reference standard, to ensure that no new peaks appear in the sample and that minor peaks do not increase above a certain threshold.
2. There is no information on how many times the column can be reused, how column performance will be evaluated and what the sample recovery from the column is.
3. The proposed acceptance criteria for stability are much different from the release acceptance criteria and are not adequate to ensure that the product does not loose efficacy over the proposed shelf-life. In fact, the sponsor proposed stability acceptance criteria based on two lots of drug product that were 30 months old. The acceptance criteria allowed for (b) (4) loss in enzyme content, when the stability acceptance criteria were compared to the release acceptance criteria.
4. The method description provided is inaccurate, in that, although the procedure to calculate the amounts of the six enzymes is described, there is no description on how to calculate the impurity peaks. Additionally, the method states that sample and (b) (4) are stable for (b) (4) after being prepared. However, the sponsor analyzed the stability of sample solutions only for 48 hrs, and no data was provided to support stability of the (b) (4).

In the original submission, the sponsor did not provide adequate information related to process validation. In the resubmission, the sponsor provided a retrospective process validation study and indicated that a prospective process validation will be conducted, for each strength, on the first three lots that will be manufactured in the future. While this procedure may be appropriate for small molecules, protein products are very complex, and in order to ensure that a high quality product is consistently manufactured, the Division of Therapeutic Proteins has requested that the process be validated prior to approval of a supplement or of an original NDA. This practice has been implemented for all PEP NDAs approved to date, as well as for traditional biotech NDA, and DCI should provide prospective process validation reports to support approval of the NDA.

The data provided in the original NDA submission to support the stability of the drug product raised concerns with the reviewer and the sponsor was asked to provide additional information. The major stability issues related to the dissolution profile of the (b) (4) 8000U lipase. (b) (4), and during the review cycle it was noted that only the 16000U was used in the clinical trial. In the resubmission, the sponsor (b) (4) provided stability data and requested (b) (4) expiration date for the (b) (4) 8000U. However, the sponsor only provided 9 months stability data for the (b) (4) 8000U strength. Expiration dating for protein products is based on data acquired during real-time, real-temperature stability studies (ICHQ5C). The sponsor should provide stability data to support the requested expiry. Overall, the data provided so far show a more favorable stability profile for the new (b) (4) 8000U strengths.

DCI provided revised release and stability acceptance criteria. The sponsor updated the release testing strategy to include assays to monitor particle size, weight of pellets/capsule and disintegration time. The assays and proposed acceptance criteria are adequate. However some of the proposed acceptance criteria are still inadequate, in that the sponsor set a limit, not a range, for amylase and protease potency, for both release and stability testing. Furthermore, the stability acceptance criterion for lipase activity is (b) (4) the release criterion, without adequate justification or data supporting the choice. The RP-HPLC acceptance criteria were discussed above. The sponsor did not provide release and stability data using the RP-HPLC assay and it is unclear whether the assay has been implemented. The sponsor should provide available release and stability data that include the RP-HPLC assay.

DCI provided a qualification program for the drug product reference standard, which we found to be inadequate. The sponsor did not include RP-HPLC in the set of assays used to qualify a new reference standard and the acceptance criteria used are the same as release testing. The qualification program for the reference standard must be rigorous and acceptance criteria should be (b) (4) release, to avoid introducing drift in the product over time.

All the other issues identified in the CR letter have been adequately addressed and the major points are summarized below.

1. The sponsor provided updated acceptance criteria for (b) (4) where the individual peaks are measured separately rather than bulked together. The proposed acceptance criteria are acceptable.

2. The sponsor provided stability studies that addressed the stability of the products under conditions of use by the patients. The study was conducted by opening the bottles several time a day for up to 60 days, and evaluating critical product attributes at 15, 30 and 60 days. The attributes measured did not vary substantially, but the study was conducted at controlled temperature and humidity. More informative were the photostability and forced degradation studies, which showed that the product is relatively stable at higher temperature and humidity (40°C and 75% relative humidity). The quality profile, and in particular dissolution and LOD, was already affected at the 10-day point. However, it is conceivable that short-time temperature excursions are not likely to negatively impact the quality of the product. Appropriate information to this effect can be provided ion the Package Insert and Medication Guide.
3. The sponsor provided data to support (b) (4) homogeneity of drug substance 1206 and drug substance 1208.
4. DCI provided data demonstrating that sufficient amounts of (b) (4) are present to ensure maximal lipase activity. The study conducted provided for addition of purified (b) (4) in pancrelipase preparation. The data showed that lipase activity did not increase with addition of (b) (4), indicating that lipase was already saturated with endogenous (b) (4).
5. The sponsor characterized the olive oil from two different vendors by Thin Layer Chromatography and RP-HPLC. The sponsor is now using the RP-HPLC method to evaluate the olive oil and is setting acceptance criteria for 15 characteristic peaks, to be compared to an olive oil reference standard.
6. The sponsor provided an adequate qualification program for the drug substance 1206 and 1208.
7. The sponsor has developed an internal reference standard.
8. All other issues pertaining to assay validation, raw materials, and Certificate of Analysis of raw materials have been adequately addressed.

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EMANUELA LACANA
01/21/2011

BARRY W CHERNEY
01/21/2011

**ONDQA Pre-Marketing Assessment Division II
Branch III
NDA Consultation #3 - Quality Assessment**

1. **NDA number: 22-175**
2. **OND Division: HFD-180**
3. **Applicant Name and Address:**

Digestive Care
1120 Win Drive
Bethlehem, PA 18017

4. **Drug Reviewed:** PANCRECARB® (Pancrelipase) delayed release capsules.
5. **Purpose of Consultation:** To review the dissolution information submitted in the original NDA and in responses to CMC questions submitted on 17-MAR-2009 and on 24-JUN-2009.
6. **Conclusion/Recommendation:** The analytical procedures used for dissolution testing, dissolution acceptance criteria, and dissolution release and stability data were reviewed. The findings are listed below:

- The dissolution limit of (b) (4) (Q) in 30 minutes proposed by Digestive Care is found **NOT ACCEPTABLE**.
- A 24 month expiration dating period when stored at controlled room temperature, as proposed in the application is **ACCEPTABLE**.

Bogdan Kurtyka, Ph.D.
Review Chemist, Branch III
Premarketing Assessment Division II
ONDQA

Date

Moo-Jhong Rhee, Ph.D.
Chief, Branch III
Premarketing Assessment Division II
ONDQA

Date

Review notes

The drug product PANCRECARB® consists of a capsule filled with delayed release minitablets (enteric coated) containing Pancrelipase USP and compendial excipients. (b) (4) strengths are proposed: (b) (4) MS-8 with 8,000 USP Units Lipase per capsule, and MS-16 with 16,000 USP Units Lipase per capsule. The proposed containers include 100 and 250 count HDPE bottles (b) (4). The applicant proposes 24 months of expiration dating period for the drug product.

This review deals with all parts of NDA 22-222 related to dissolution as follows:

- analytical procedure used for dissolution,
- reference standards,
- acceptance criteria for dissolution in the drug product specification, and
- dissolution data for samples on stability testing.

Dissolution Analytical Procedure TM-6007

As stated in Consultation Review #1, the method is **ACCEPTABLE**.

Reference Standards

As stated in Consultation Review #1, the reference standard is **ACCEPTABLE**.

Drug Product Specification

In the original application Digestive Care proposed a limit of NLT (b) (4) (Q) in 30 minutes for buffer stage lipase dissolution at release and on stability. This value is significantly (b) (4) the limit in the USP monograph on Pancrelipase Delayed-Release Capsules, where it is set for 75% (Q) in 30 minutes. Additional data to justify the limit were submitted on 17-MAR-2009. However, the reviewer did not find the justification appropriate to support the limit of NLT (b) (4) (Q) in 30 minutes. However, the applicant was informed that based on the submitted information a limit of NLT (b) (4) (Q) in 30 minutes would be acceptable. For details see the Consultation #2. In the amendment under review Digestive Care proposes to set the dissolution limit at NLT (b) (4) (Q) in 30 minutes. The unique justification for the limit is quoted verbatim as follows:

The DCI dissolution limit is based on controlled clinical study 06-001 in which the initial release dissolution result was (b) (4) for Lot 6K90B. The same lot was used in the bioavailability study 092206. Since (b) (4) is the starting point for dissolution and the USP provides a lower limit of (b) (4), DCI proposes a (b) (4) specification of (b) (4). These data along with the results of clinical trial 06-001 support the proposed (b) (4) limit throughout the shelf-life of the drug product.

Evaluation: The presented justification would be valid under assumption that at 30 minutes the dissolution process is complete and the dissolution value lower than 100% is the result of activity lost during the test procedure. This was not demonstrated by Digestive Care. The justification is based on manipulation of numbers which happened to yield the product close to (b) (4). The dissolution limit of (b) (4) (Q) in 30 minutes proposed by Digestive Care is found **NOT ACCEPTABLE**.

Stability Results for Dissolution

The amendment under review includes the update of stability data for dissolution as follows (only the long term condition listed):

- (b) (4)
- MS-8: 24 months for 2 lots and 12 months for 1 lot
- MS-16: 24 months for 3 lots

The applicant proposes 24 months expiration dating period when stored at the controlled room temperature.

Evaluation: The analysis of the dissolution data is done using the dissolution limit of NLT (b) (4) (Q). All dissolution results throughout the study remain within this limit for all (b) (4) strengths. Dissolution trends in two lots with data spanning less than 24 months (b) (4) one lot of MS-8) are similar to these for the remaining lots. Based on the submitted data 24 months expiration dating period when stored at the controlled room temperature proposed in the application is **ACCEPTABLE**.

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Bogdan Kurtyka
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CHEMIST

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Moo-Jhong Rhee
7/22/2009 04:11:11 PM
CHEMIST
Chief, Branch III

The Chemistry Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Division of Therapeutic Proteins, Office of Biotechnology Products, OPS, CDER, does not recommend approval of NDA #22-175 for pancrelipase manufactured by Digestive Care Inc. The data submitted in this application do not support the conclusion that the manufacture of pancrelipase is controlled, and leads to a product that is consistent and potent. Issues that preclude approval of this application include inadequate release and stability testing, inadequate process validation and inadequate stability data to support an assignment of expiry.

B. CMC deficiency comments:

1. Your release testing program is inadequate. Specifically, we have identified the following deficiencies:
 - a. You have not included an analytical test to control for product-related and process-related impurities. Product and process-related impurities should be monitored and appropriate acceptance criteria, based on process capability, manufacturing history and clinical experience should be developed and implemented. An analytical methodology such as, but not limited to, HPLC would be suitable to assess the purity of your product.
 - b. You have not included analytical tests to monitor particle size, target weight of pellets/capsule and capsule disintegration time. Appropriate analytical methodologies should be used and acceptance criteria established.
2. Your stability program does not provide assurance that product stability is adequately controlled. Specifically, we have identified the following deficiencies:
 - a. You have not included analytical techniques that monitor product degradation such as, but not limited to, HPLC.
 - b. The acceptance criterion for lipase activity should be revised to include an upper and lower limit.

- c. The stability data you have provided indicate that some drug product lots show a clear (b) (4) trending in the dissolution profile over a 12-month period whereas some other lots maintain a stable dissolution profile. Please provide an explanation for these inconsistencies in the stability data.
- d. You are currently reporting (b) (4) content as a combination of all solvents measured. Please provide acceptance criteria for each of the (b) (4) separately.
- e. Expiry dating for a protein product is based on real-time and real-temperature stability data. You have not provided real-time stability data to support a 24 month expiry.
- f. Please provide your rationale for using (b) (4), in addition to gelatin capsules, and justify why additional stability or clinical data are not necessary.
- g. You have not provided a study that addresses the stability of the product once the final container is opened in the pharmacy or by the patient. Please provide forced degradation studies (i.e. photostability, moisture conditions, etc.) conducted on the drug product to support in-use stability of drug product.
- h. Please update your stability protocol to include (b) (4) testing at all test stations.
3. You have not provided sufficient information to the Agency to evaluate the reprocessing steps in your manufacturing process. Please provide studies you have conducted and documentation of procedures you have in place to support reprocessing.
4. You are (b) (4) drug substances manufactured by different processes (1206 and 1208) to achieve a defined target lipase activity. However, you have not provided sufficient information to evaluate whether the (b) (4) step in your manufacturing process will result in a homogeneously (b) (4) drug substance. Please provide validation studies that address the homogeneity of the (b) (4) drug substance used to manufacture (b) (4) MS8 and the homogeneity of the (b) (4) drug substance used to manufacture MS16.
5. Due to the critical role of (b) (4) in lipase activity, adequate control of (b) (4) activity must be ensured in drug product. Please

provide information that demonstrates you have control of (b) (4) activity in drug substance and product.

6. You have not submitted sufficient information in the NDA to evaluate your qualification program for the lipase olive oil substrate. Please provide qualification results for olive oil testing, and establish and justify specifications for critical olive oil components.
7. Please provide a description of your qualification program for incoming 1206 and 1208 drug substances.
8. We recommend that an internal reference standard that reflects the drug product commercial manufacturing process be used, in addition to the pancrelipase drug substance reference standard, in all release and stability testing. Please develop a rigorous qualification program aimed at ensuring that the quality attributes of the internal reference standard are maintained when new internal reference standards are required and manufactured.
9. Due to the potential inconsistencies and reliance on the USP lipase reference standard, we recommend the development and implementation of a method that includes a measurement of absolute units to ensure accurate and consistent lipase activity for the working reference standard.
10. In regards to your analytical methodologies, we have the following comments:
 - a. The assessment of linearity for the lipase and protease assays is conducted using (b) (4) data points. We recommend a minimum of 5 data points for determination of assay linearity.
 - b. Please clarify your acceptance criteria for lipase assay linearity.
 - c. To support validation of (b) (4) assay precision, please clarify the amounts of (b) (4) used during assay validation.
11. Please provide detailed information regarding the chemistry, manufacturing and controls for the cellulose acetate phthalate and diethyl phthalate used for (b) (4) of the product.
12. Please provide the drug product release test sampling plans.

13. Please provide a comparison of the formulation of the To be Marketed Product (TbMP) and the Currently Marketed Product.
14. We do not have sufficient information to evaluate your process validation. Please provide the following information:
 - a. The process validation report, with all relevant supporting data to demonstrate that your process is adequately controlled.
 - b. Clarify the method used to assess the yield in (b) (4) of drug product manufacturing.
15. Please provide representative vendor COAs and your testing results of the excipients used in the manufacturing of (b) (4) MS-8 and MS-16.
16. The DMF you have referenced for the (b) (4) Ink, DMF (b) (4), is closed. Please provide CMC information, including iron content, for (b) (4) Ink.
17. We noticed discrepancies between the manufacturing dates of drug products lots, and the dates the Certificate of Analyses were signed. In some cases, over two years elapsed between manufacturing and CoA sign off. Please explain these discrepancies.

II. Summary of Chemistry Assessments

Description of the Drug Product(s) and Drug Substance(s)

- **General:** Pancrelipase is the USAN name for the active pharmaceutical ingredient in PANCRECARB®, and is a complex mixture of proteins obtained from porcine pancreas. Pancrelipase contains amylase, lipase, and (b) (4).
(b) (4)
- **Drug Product Presentation:** PANCRECARB® is administered orally in gelatin capsules. Each capsule contains enteric coated pancrelipase microspheres. The capsules are packaged in high density polyethylene bottles. PANCRECARB® is presented in (b) (4) strengths, based on lipase activity. They are (b) (4), MS-8, and MS-16 contain (b) (4) 8000, and 16000 USP units respectively. Pancrelipase is formulated with sodium carbonate (b) (4), sodium bicarbonate, sodium starch glycolate, ursodiol, polyvinylpyrrolidone, cellulose acetate phthalate, diethyl phthalate, and talc. (b) (4)
(b) (4) Cellulose phthalate and diethyl phthalate (b) (4)
(b) (4) These chemicals are all USP/NF grade. The coated

product dissolves at the higher pH in the intestine, thereby releasing the pancreatic enzymes in the site of action.

- Complexity: As described above, the product is a complex mixture of different proteins present in the pancreatic extracts. The sponsor of this NDA purchases the drug substance from (b) (4) (DMF (b) (4)).
- Biological activity: Pancrelipase functions to replace pancreatic enzymes, which are absent in patients with cystic fibrosis or pancreatic insufficiency. The enzymes contained in pancrelipase are active in the intestinal environment, where they contribute to the digestion of fats, carbohydrates and proteins in food. Lipase, amylase and proteases are all considered active ingredients in pancrelipase. However, clinical efficacy has been demonstrated only for lipase. (b) (4)
(b) (4) The sponsor has yet to demonstrate that the (b) (4) level in this product is well controlled.
- Potency Assays to Measure Activity. Three assays are used to assess pancrelipase potency and these assays measure lipase, amylase and protease activities. All assays are performed based on established USP methods. Enzymatic assays measure the conversion of a specific enzyme substrate into a product. The substrate used in the lipase assay is olive oil. The triglycerides contained in the olive oil are hydrolyzed to free fatty acids, and the enzymatic activity is measured by sodium hydroxide titration of the free fatty acids generated. Lipase activity is calculated by comparing the rate of olive oil hydrolysis by the drug substance or drug product to the rate of olive oil hydrolysis by a pancrelipase reference standard. Starch is the substrate used in the amylase activity assay and reacts strongly with iodine, turning a deep blue color. Digestion of starch by amylase is measured by a reduction in color intensity and the amylase activity is measured by comparing the starch hydrolysis rate by the drug substance or product to the starch hydrolysis rate by a pancrelipase reference standard. Protease potency is measured using casein as a substrate. Casein digestion by protease generates peptides that are soluble after acid treatment of the reaction mixture, in contrast to casein protein, which is insoluble. The precipitated casein is removed and the amount of soluble peptides is measured by absorbance at 280 nm. Protease activity is calculated by comparing the casein hydrolysis rate by the drug substance or product to the casein hydrolysis rate by a pancrelipase reference standard. In regards to the lipase assay, the sponsor did not provide an appropriate qualification program for the olive oil substrate, which is critical for lipase activity measurement.
- Manufacturing of Drug Substance and Product: Pancrelipase drug substance is manufactured by processing of porcine pancreases. The glands (about (b) (4) of drug substance) are (b) (4)

- Drug Product Release Tests:

The release tests for drug product include: appearance, identity by enzyme activity (lipase, protease and amylase) and SDS-PAGE, impurities (b) (4), and potency by enzyme activity (lipase, protease and amylase) and dissolution. The drug product release testing is inadequate, in that there are no tests for product degradants or tests used to monitor particle size, target weight of pellets/capsule and capsule disintegration time.

Critical Product Attributes:

- i. Lipase activity: Lipase activity is a critical product attribute linked to both safety and efficacy, and is used to assess potency. Excessive lipase potency has been correlated to fibrosing colonopathy in children younger than 12 years of age and the primary efficacy endpoint in clinical studies was the Coefficient of Fat Absorption, which is linked to lipase activity. The lipase assay methodology is deficient and a qualification protocol for the olive oil substrate needs to be developed and implemented. In addition to the USP reference standard used in the assay, an internal standard needs to be developed that is representative of the commercial drug product process.
- ii. Moisture: Pancrelipase is sensitive to moisture and lipase activity is rapidly lost upon exposure to moisture.
- iii. Dissolution: Dissolution of microspheres is essential for release of pancreatic enzymes in the intestine, the site of therapeutic action.
- iv. Microbial content: Tests performed on the drug substance and drug product to ensure microbial control include total aerobic microbial

count, total combined yeasts and mold counts, and the absence of Salmonella and Escherichia coli.

- Degradation and Stability. Pancrelipase is particularly sensitive to moisture. Lipase activity is quickly lost by exposure to moisture (b) (4). The sponsor is requesting a drug product shelf life of 24 months when stored at 25°C. The data provided by the sponsor do not support this request. The dissolution profile over time varies considerably, with some lots maintaining a stable profile and other lots with a clear (b) (4) trend (b) (4).

Description of How the Drug Product is Intended to be Used

- PANCRECARB® is indicated for the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions. PANCRECARB® is orally administered. Therapy should be initiated at the lowest recommended dose. The dosage of PANCRECARB® should be individualized based on clinical symptoms and the fat content of the diet. Patients may be dosed on a fat ingestion-based or actual body weight-based dosing scheme, as outlined below:

DOSE OF PANCRECARB®	
<i>Age of patients</i>	<i>Dose (lipase, in USP units)</i>
(b) (4)	
Children 12 months-4 years	^a 1,000-2,500 units/kg/meal or, ≤10,000 units/kg/day or, < 4,000 lipase unit/g fat/day
Children 4 years and older and adults	500-2,500 units/kg/meal or, ≤10,000 units/kg/day or, < 4,000 lipase unit/g fat/day

^a Represent the recommended lowest starting dose of PANCRECARB® for the patient group

- PANCRECARB® is supplied in gelatin capsules with the following lipase strength/capsule: (b) (4) 8,000 and 16,000 USP U/cap. PANCRECARB® capsules are contained in bottles with 100 and 250 counts each for MS-8 and MS-16. (b) (4)

Submission: NDA 22175
Product: PANCRECARB® (pancrelipase) Capsules; (b) (4) MS-8, MS-16
Indication: Exocrine pancreatic insufficiency
Formulation: Oral, capsule, enteric coated microspheres

Date: October 28, 2008
Sponsor: Digestive Care, Inc.

CMC Reviewer: Wei Guo, Ph.D., HFD-122
Through: Emanuela Lacana, Ph.D., HFD-122, Associate Chief, Lab of Chemistry
Gibbes Johnson, Ph.D., HFD-122, Chief, Lab of Chemistry
Barry Cherney, Ph.D., HFD-122, Deputy Director, DTP
Review Date: June 5, 2009

Conclusion: The Division of Therapeutic Proteins does not recommend approval of this NDA submission, due to CMC issues that cannot be resolved in this review cycle. A number of comments were sent to the sponsor in a review discipline letter and will also be sent in a Complete Response letter. These comments and the additional comments identified upon completion of the review will be finalized in the Executive summary.

CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

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INTRODUCTION

Digestive Care, Inc. submitted IND 45223 on April 26, 1994. NDA 22175 was submitted in October 2008.

This review is focused on CMC only. Critical assessment will be written in italic, comment will be written in bold.

This submission is CTD formatted, and is reviewed as such.

3.2.S DRUG SUBSTANCE

The sponsor referenced DMF (b) (4) for drug substance. It is stated that both 1206 and 1208 drug substances made by (b) (4) are used as drug substance to support this NDA.

Authorization letter dated September 2008 is provided. A facility inspection was conducted in (b) (4). FDA Form 483 with (b) (4) observations was issued. Determination of GMP status will be made after reviewing the firm's response to all the findings.

Note: GMP status of DMF holder is under evaluation.

3.2.P DRUG PRODUCT

Drug product CMC information is provided in CTD format, and is reviewed accordingly.

3.2.P.1 DESCRIPTION AND COMPOSITION

All manufacturing and testing of the drug product are conducted at Digestive Care Inc. (DCI).

PANCRECARB® (pancrelipase) Capsules are intended for the treatment of Exocrine Pancreatic Insufficiency. The three strengths of this product (MS-4, MS-8 and MS-16) have been marketed in the United States since 1995, 2000, and 2004 respectively.

PANCRECARB® (pancrelipase) Capsules are solid oral dosage form comprised of clear gelatin (b) (4) capsules containing small enteric-coated microspheres of buffered pancreatic enzymes (lipase, amylase and protease). Pancreatic enzymes are isolated and concentrated from porcine pancreatic glands. The manufacturing of pancrelipase drug substance is described in DMF (b) (4)

PANCRECARB® Capsules are manufactured in (b) (4) strengths:

Product	Lipase	Amylase	Protease
	(b) (4)	(b) (4)	(b) (4)
MS-8	8,000 USP units		
MS-16	16,000 USP units		



The complete composition of the drug product is:

INGREDIENTS	mg/Capsule		% w/w		Function
	MS-8	MS-16	MS-8	MS-16	
Pancrelipase, USP 1206 (b) (4) 1208	(b) (4)	(b) (4)	(b) (4)	(b) (4)	Active Ingredient
Sodium Carbonate (b) (4) NF					(b) (4)
Sodium Bicarbonate, USP					
Sodium Starch Glycolate, NF					
Ursodiol, USP					
Polyvinylpyrrolidone, USP					
Cellulose Acetate Phthalate, NF					
Diethyl Phthalate, NF					
Talc, USP (b) (4)					
TOTAL MASS			100.0	100.0	

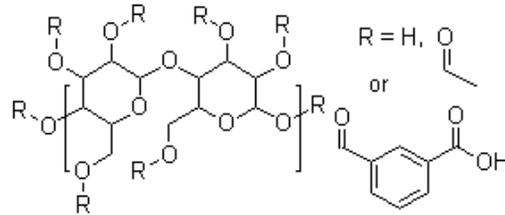
** Adjusted based on lipase activity

The firm stated that Sodium carbonate/sodium bicarbonate-buffer is used in the formulation to keep lipases at their optimal pH for maximum enzymatic activity. Ursodiol is included in the formulation as an aid to enhance the wetting and the release of pancrelipase from the microspheres.

The microspheres are (b) (4) enteric coating to protect the enzymes from acidic gastric inactivation during gastric passage.

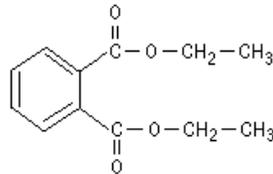
Cellulose Acetate Phthalate, NF:

(b) (4) The chemical structure is given below:



Diethyl phthalate, NF:

It is a colorless liquid with a slight aromatic odor. (b) (4)
Its structural formula is given below.



Chemical structure of Diethyl phthalate, NF ($C_{12}H_{14}O_4$; Mw: 222.3; CAS No. 84-66-2)

The safety of these two chemicals will be evaluated by the Pharm/Tox reviewer. The manufacturing process of these two chemicals is not provided in the submission and no DMF is referenced.

Comment: Please provide detailed information regarding the chemistry, manufacturing and controls for the Cellulose acetate phthalate and Diethyl phthalate used for (b) (4) of the product.

The active ingredient represents (b) (4) of the weight of each coated pellet. The coated microspheres are filled into clear, hard gelatin (DMF (b) (4)) or (b) (4) the size of the capsules and color imprint are listed below:

Formulation	Size of Hard Gelatin Capsule	Capsule Imprint (Top/Bottom)	Color of Imprint
			(b) (4)
MS-8			Blue
MS-16			Red

The sponsor stated that stability studies are currently in progress to determine the shelf-life of the microspheres in clear, hard, (b) (4) capsules. (b) (4)

(b) (4)

(b) (4)

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

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**ONDQA Pre-Marketing Assessment Division II
Branch III
NDA Consultation #2 - Quality Assessment**

1. **NDA number:** 22-175
2. **OND Division:** HFD-180
3. **Applicant Name and Address:**

Digestive Care
1120 Win Drive
Bethlehem, PA 18017

4. **Drug Reviewed:** PANCRECARB® (Pancrelipase) delayed release capsules
5. **Purpose of Consultation:** To review the dissolution information submitted in the original NDA and in responses to CMC questions submitted on 17-MAR-2009.
6. **Conclusion/Recommendation:** The analytical procedures used for dissolution testing, dissolution acceptance criteria, and dissolution release and stability data were reviewed. The findings are listed below:

- The modified USP procedure for dissolution is found **ACCEPTABLE**.
- The dissolution limit of (b)(4) (Q) in 30 minutes proposed by Digestive Care is found **NOT ACCEPTABLE**. Based on the submitted information a limit of (b)(4) (Q) in 30 minutes would be acceptable.
- A 24 month expiration dating period when stored at controlled room temperature, as proposed in the application is **NOT ACCEPTABLE**. The recommended expiration dating period based on the submitted data is (b)(4) (b)(4) for formulations MS-8 and MS-16. This expiration dating period can be extended as more stability data are available.

The following comments should be conveyed to the applicant:

- The submitted data do not support the proposed dissolution limit of (b)(4) (Q) in 30 minutes. However, based on the provided information a limit of (b)(4) (Q) in 30 minutes would be acceptable.
- A 24 month expiration dating period when stored at controlled room temperature, as proposed in the application is not justified. Based on the acceptable dissolution limit of (b)(4) (Q) an expiration dating period of (b)(4) (b)(4) for formulations MS-8 and MS-16 could be granted.

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Review notes

The drug product PANCRECARB® consists of a capsule filled with delayed release minitables (enteric coated) containing Pancrelipase USP and compendial excipients. (b) (4) strengths are proposed: (b) (4) MS-8 with 8,000 USP Units Lipase per capsule, and MS-16 with 16,000 USP Units Lipase per capsule. The proposed containers include 100 and 250 count HDPE bottles (b) (4) The applicant proposes 24 months of expiration dating period for the drug product.

The current review deals with all parts of NDA 22-222 related to dissolution as follows:

- analytical procedures used for dissolution,
- reference standards,
- acceptance criteria for dissolution in the drug product specification,
- dissolution data for samples on stability testing.

Dissolution Analytical Procedure TM-6007

In responses to CMC questions Digestive Care states that deviation from the original USP dissolution method was introduced (b) (4)

The deviation consisted of addition of olive oil substrate, casein substrate, and starch substrate to the phosphate buffer medium (b) (4) The deviation is found justified.

Another difference between the USP and the proposed method is in duration of the acid phase test, which is 30 minutes in the proposed method and 60 minutes in USP monograph. This difference is justified based on the submitted data which show that enzyme activity lost in the acid stage is comparable for 30 and 60 minutes. The method is **ACCEPTABLE**.

Reference Standards

As stated in Consultation Review #1, the reference standard is **ACCEPTABLE**.

Drug Product Specification

The applicant proposes a limit of NLT (b) (4) (Q) in 30 minutes for buffer stage lipase dissolution at release and on stability. This value is significantly (b) (4) the limit in the USP monograph on Pancrelipase Delayed-Release Capsules, where it is set for 75% (Q) in 30 minutes. In justifying the dissolution limit the applicant takes into consideration partial loss of enzymatic activity during the buffer stage of dissolution. In addition the applicant states that the dissolution limit is justified by the effectiveness of the drug demonstrated during the clinical trials, in particular by lot 6K09B (the lot used in pivotal trials). Lot 6K09B was analyzed on release with an assay value of (b) (4) and dissolution of (b) (4) in 30 minutes.

Pivotal trials started in February 2007 and concluded in September 2007. Lot 6K09B was manufactured in November 2006, and the stability data indicate that dissolution result was (b) (4) in August 2007 and (b) (4) in November 2007. The data show that during pivotal trials Lot 6K09B was characterized by dissolution values (b) (4) than the (b) (4) (Q) proposed by applicant. Therefore justification of the proposed (b) (4) dissolution limit based on samples shown to be safe and effective in the pivotal studies is not justified since the material used in the trials showed at worst, approximately (b) (4) dissolved.

The data submitted by Digestive Care to support proposed dissolution limit based on activity loss during the dissolution experiment indicate that the dissolution result is always (b) (4) that the corresponding lipase assay. Digestive Care attributes this difference to the activity lost.

However, this interpretation implies that dissolution is complete in 30 minutes, which is not supported by the data. The USP monograph on delayed release Pancrelipase capsules specifies the assay limit as 90%, and dissolution limit as 75% in 30 minutes, allowing for a 15% difference. Taking into consideration that the drug product under review shows this difference between (b) (4) it appears that applying the dissolution limit (b) (4) the USP limit is warranted. However, the limit of (b) (4) (Q) in 30 minutes proposed by Digestive Care is not justified and **NOT ACCEPTABLE**. However, based on the submitted information a limit of (b) (4) (Q) in 30 minutes would be acceptable.

Stability Results for Dissolution

The analysis of the dissolution data is done in the context that (b) (4) (Q) dissolution is acceptable (as explained above) and any lower values are not. The submitted data suggest that only the first stage of dissolution test was performed (6 tablet based stage S1), so the limit of (b) (4) (Q + 5%) applies in compliance with the USP dissolution procedure.

Formal stability studies were performed using the proposed commercial container/closure system. The applicant proposes 24 months expiration dating period when stored at the controlled room temperature. The following stability data were submitted:

- 12 months data at long term condition, 12 months data at intermediate condition and 6 months data at accelerated condition are provided for three batches (b) (4) MS-16 in 100 count bottles (lot 6K09B of MS-16 18 months long term data).
- 12 months data at long term condition, 12 months data at intermediate condition and 6 months data at accelerated condition are provided for two batches of MS-8 in 100 count bottles. 3 months data at all conditions are provided for a single batch of MS-8 in 100 count bottles. This deviation from minimum time period of stability data recommended by ICH (3 batches, 12 months long term and 6 months accelerated) is acceptable (b) (4)
- 12 months data at long term condition are provided for one batch of MS-8 in 250 count bottle. (b) (4)

Since the proposed storage is at controlled room temperature, stability data at refrigerated conditions (12 months submitted) are not taken into consideration. This evaluation applies to drug product in gelatin capsules in 100 and 250 count bottles.

In the evaluation of stability data the approach recommended in ICH Q1E was used. The observed stability trends are as follows:

- At the accelerated condition all stability lots show significant change at 3 or 6 months.
- At the intermediate condition some lots show significant change. Lots 7A02A and 6K09B show the 3 months dissolution values to be below the (b) (4) (Q) dissolution limit, but return to acceptable values at 6 months. This behavior is not considered a significant change, and may be attributed to measurement error. However, the following lots show results (b) (4) (Q) limit, follow a clear (b) (4) trend, and are considered real significant changes:
 - Lot 7B03A of MS-8 shows dissolution at (b) (4) at 12 months
 - Lot 7D05A of MS-8 shows dissolution at (b) (4) at 9 months and at (b) (4) at 12 months
 - Lot 6K09B of MS-16 shows dissolution at (b) (4) at 12 months

- At the long-term condition none of the lots showed significant change. Most of them showed dissolution to be at (b) (4) at 12 months. However, two lots of MS-16 (7A01B and 6K09B) show the result at the limit of (b) (4) at 12 months (equivalent to (b) (4) (Q)).

The analysis of dissolution data shows that the stability of the drug product depends on capsule size (b) (4)

Two lots of formulation MS-8 show significant changes at the intermediate condition, but the changes occur after 6 months (the ICH time period for intermediate data). This reviewer considered granting (b) (4) expiration dating for MS-8 based on trends in long-term data. However, since only two batches with 12 months of long-term data were submitted, an expiration dating period of (b) (4) is recommended.

Formulation MS-16 appears to be the least stable. One lot shows significant changes at the intermediate condition (at 12 months). In addition, two lots show a long-term dissolution result at the (b) (4) limit at 12 months. (b) (4)

24 months expiration dating period when stored at the controlled room temperature proposed in the application is **NOT ACCEPTABLE**. The recommended expiration dating period is (b) (4) for formulations MS-8 and MS-16. As updated stability data become available, it may be possible to extend these periods.

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/s/

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4/27/2009 03:18:25 PM
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**ONDQA Pre-Marketing Assessment Division II
Branch III
NDA Consultation - Quality Assessment**

1. **NDA number: 22-175**

2. **OND Division: HFD-180**

3. **Applicant Name and Address:**

Digestive Care
1120 Win Drive
Bethlehem, PA 18017

4. **Drug Reviewed: PANCRECARB® (Pancrelipase) delayed release capsules**

5. **Purpose of Consultation:** To review the dissolution information submitted in the NDA

6. **Summary:** The analytical procedures used for dissolution testing, dissolution acceptance criteria, and dissolution release and stability data were reviewed. Several issues were noted as listed below:

- Buffer stage dissolution data for drug product manufactured without an overage fall well below the USP limit of 75% dissolution of lipase in 30 minutes. This is observed both at release and in stability samples. For the pivotal clinical batch (6K09B) (b) (4) of label claim is observed for dissolution at release, which should be compared with (b) (4) of label claim for assay. For all batches, the dissolution data at release consistently show (b) (4) lipase activity than determined in the assay of the capsules, suggesting loss of activity during dissolution testing.
- The applicant has modified the dissolution medium recommended by USP for buffer stage testing by adding olive oil substrate, casein substrate, and starch substrate to the phosphate buffer medium. (b) (4)
- The applicant has (b) (4) the USP Stage 2 acceptance limit for dissolution from (b) (4) to (b) (4) dissolution of lipase in 30 minutes, justifying the new limit on the basis that the pivotal clinical trials were conducted with drug product that exhibited the (b) (4) dissolution.
- At the conclusion of acid stage dissolution testing, a loss of approximately (b) (4) is observed in enzyme activity of the product. This loss is consistently present in all samples tested. While USP allows for a (b) (4) loss of drug substance during acid stage testing, observing such consistently high results is unusual, with most products showing not more than (b) (4) if any. The data for the current product suggest that (b) (4) is compromised during acid stage testing.

7. **An IR letter with the following comments should be forwarded to the sponsor:**

- Please explain why you have modified the dissolution medium recommended by USP for buffer stage testing by adding olive oil substrate, casein substrate, and starch substrate to the phosphate buffer medium, and explain how these additional

components affect the dissolution properties of the product. Please provide data to support your arguments.

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

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Review notes

The drug product PANCRECARB® consists of a capsule filled with delayed release minitablets (enteric coated) containing Pancrelipase USP and compendial excipients. (b) (4) strengths are proposed: (b) (4) MS-8 with 8,000 USP Units Lipase per capsule, and MS-16 with 16,000 USP Units Lipase per capsule. The proposed containers include 100 and 250 count HDPE bottles (b) (4) The applicant proposes 24 months shelf life for the drug product.

The current review deals with all parts of NDA 22-222 related to dissolution as follows:

- analytical procedures used for dissolution,
- reference standards,
- acceptance criteria for dissolution in the drug product specification,
- stability results for dissolution

Dissolution Analytical Procedure TM-6007

In the meeting on 05-FEB-2007 the applicant stated that there have been problems with their dissolution testing methods, and requested a waiver from conducting dissolution testing. The Agency stated that dissolution testing is an important part of quality control testing, and the sponsor would need to propose an alternative method of quality control testing if the issues could not be resolved. In the current application the applicant states that “only moderate success has been achieved” in the method improvement, despite several attempts. The applicant states that the analytical procedure for dissolution TM-6007 is based on the method outlined in the USP monograph on Pancrelipase Delayed-Release Capsules, with some modifications. Comments on the procedure are listed below.

Dissolution testing is performed in two stages; 30 minutes in the acid phase (simulated gastric fluid), followed by 30 minutes in the buffer phase (pH 6.0 phosphate buffer with additional olive oil substrate, casein substrate, and starch substrate, called intestinal fluid in the application). The USP monograph requires that the second stage of dissolution testing be performed in phosphate buffer without any additional ingredients; olive oil substrate is only used in the testing of samples taken from the dissolution apparatus to determine enzyme content, not in the dissolution medium. Casein and starch substrates are not used in the USP dissolution procedure at all, not in the dissolution medium and not in any analytical procedures associated with dissolution. Both are utilized in amylase and protease activity assays. The purpose of adding three substrates to the dissolution medium is not discussed by the applicant. There is a concern that the addition of the substrates (in particular the olive oil substrate) in to the dissolution medium will start the digestion of lipase in the dissolution vessel, causing changes in the lipase activity, and consequently, the low dissolution values.

With regard to Stage 1 dissolution (30 minutes exposure to the simulated gastric fluid), the results from 6 repetitions show a lipase activity loss at the end of this stage ranging from (b) (4) to (b) (4), with an average of (b) (4). The (b) (4) value is above the 10% USP limit on acid phase release in delayed-release drugs (USP <711>) While the other values are within this limit, the average is unusually high for enteric-coated drugs, raising concerns about the integrity of the enteric coating and possible denaturation of drug product enzymes due to the exposure to the acid.

The above concerns were not discussed in the application as part of the justification of the dissolution limit. The proposed limit of (b) (4) in 30 minutes is significantly (b) (4) the limit in the USP monograph on Pancrelipase Delayed-Release Capsules, where it is set for 75% (Q) in 30

minutes. Considering the above findings, the analytical method described in the application is deemed **NOT ACCEPTABLE** and further communication with the applicant is necessary to resolved issues and concerns.

Reference Standards

The USP Reference Standard Pancreatin Lipase is used as a reference standard for performing the dissolution testing. The application does not specify the USP Reference Standard lot number, but method TM-6007 (dissolution) states that the current lot of the standard is used. This part is **ACCEPTABLE**.

Drug Product Specification

The applicant proposes a limit of NLT (b)(4) in 30 minutes for lipase dissolution at release and on stability. This value is significantly (b)(4) the limit in the USP monograph on Pancrelipase Delayed-Release Capsules, where it is set for 75% (Q) in 30 minutes. In justifying the dissolution limit the applicant states that there are unresolved issues with the dissolution test, but does not explain what these issues are. However, according to the applicant, the dissolution limit is justified by the effectiveness of the drug demonstrated during the clinical trials, in particular by the lot 6K09B (the lot used in pivotal trials). The applicant also includes a table that shows lipase assay and dissolution results (at release) for all clinical batches, as follows:

Clinical Study	1 Lot #	2 Net Wt./Cap in mg.	3 Specific Activity Lipase Unit/mg.	4 Total Lipase Units (Col. 2 x Col. 3 = Col. 4)	5 Dissolution of Lipase @ pH 6.0 @ 37°C, 30 min. Units/mg.	6 Total Lipase Units on Dissolution (Col. 2 x Col. 5 = Col. 6)
MS-8						(b)(4)
111395						
111395, 020296						
97-001-1B						
97-001-1B, 97-001-2						
97-001-1B						
97-001-2						
97-001-1B, 091897						
091897						
092100						
Mean (SD)						
MS-16						(b)(4)
06-001, 092206						
071503						

The analysis of the table shows the following:

- The majority of batches show a large difference between lipase assay and dissolution results, in most cases (b)(4) but most clinical batches were manufactured with a significant overage of the drug substance, up to (b)(4).

- Lot # 6K09B, proven effective in the pivotal trial, has dissolution result of (b) (4), very close to the USP limit. It is also noted that this particular lot has been manufactured at the highest strength of the drug (MS-16).

Overall, the applicant's justification of the dissolution limit is considered insufficient at the present time to support the value of (b) (4). Responses to the questions posed in the IR letter (see item 7, above) may provide additional insight. **NOT ACCEPTABLE.**

Stability Results for Dissolution

Formal stability studies were performed using the proposed commercial container/closure system. The applicant proposes 24 months shelf life when stored at the controlled room temperature.

- 12 months data at long term condition, 12 months data at intermediate condition and 6 months data at accelerated condition are provided for three batches (b) (4) MS-16 in 100 count bottles.
- 12 months data at long term condition, 12 months data at intermediate condition and 6 months data at accelerated condition are provided for two batches of MS-8 in 100 count bottles. 3 months data at all conditions are provided for a single batch of MS-8 in 100 count bottles.
- 12 months data at long term condition are provided for one batch of MS-8 in 250 count bottle (b) (4)

It is premature to evaluate the stability data until the questions regarding the methodology and limits are resolved.

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