CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-175Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

ONDQA BIOPHARMACEUTICS REVIEW

NDA:	22-175 Resubmission
Resubmission Date:	11/15/11
Other Submissions Dates:	02/07/12, 02/21/12, 03/07/12, and 04/10/12
Brand Name:	Pertzye
Generic Name:	Pancrelipase
Formulation:	Delayed release (DR) capsule
Strength:	8,000 and 16,000 lipase units/capsules
Applicant:	Digestive Care Inc. (DCI)
Type of submission:	Original (N-000)
Reviewer:	Tien-Mien Chen, Ph.D.

SYNOPSIS

Background: Original NDA 22-175 was submitted on 10/27/08 by Digestic Care Inc. (DCI), seeking approval for Pertzye (pancrelipase) DR capsule, (b) (4) 8,000 (MS8), and 16,000 (MS16) lipase units/capsules. In the original submission, only the highest 16,000 lipase unit-strength was tested clinically. For the proposed (b) (4) 8,000 lipase unit-strengths, (b) (4) . On 08/27/09, FDA issued a complete response (CR) letter for this NDA.

On 07/29/10, DCI resubmitted NDA 22-175 with their responses to the deficiencies included in the CR letter. In the resubmission, DCI included (b) (4) composition and proportion for the (b) (4) 8,000, and 16,000 lipase units/capsule (% w/w), making the (b) (4) proposed strengths (b) (4). During the 2nd review cycle, the dissolution testing/data for the (b) (4) proposed strengths, plus the developed dissolution methodology and the proposed dissolution acceptance criterion were reviewed. The labeled activity (potency) of (b) (4) to (b) (4) was obtained, whereas, the dissolution results showed that at month "Zero", the mean % of lipase dissolved/released at 30 min only accounted for (b) (4) of the labeled lipase activity (potency) for all the (b) (4) strengths. The sponsor did not fully justify the loss of the activity during the dissolution testing. On 01/27/11, FDA issued a 2nd CR letter for this NDA. The CR included the Biopharmaceutics pending issues as additional comments.

Current Submission: On 11/15/11, DCI resubmitted NDA 22-175 for its 3rd review cycle. In this resubmission, the Applicant decided to pursue (b) (4) 8,000 IU and 16,000 IU lipase units/capsule.

Biopharmaceutics Review: The Biopharmaceutics review is focused on 1). The evaluation and approvability of the dissolution method, 2). The proposed dissolution acceptance criterion for lipase (only), and 3). The biowaiver request for the lower strength, MS8.

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ONDQA-Biopharmaceutics has evaluated the overall information included in the 2nd resubmission as well as the additional information provided in the Applicant's responses to the FDA's Information Request Letters dated 01/20/12 and 02/23/12 and teleconference held on 02/22/12, and to the further information requests dated 02/23/12, 03/07/12, and 03/30/12.

ONDQA-Biopharmaceutics has the following comments:

1. The standing issue for low recovery of lipase activity during dissolution testing has been resolved.

2. The applicant provided comparative dissolution data/profiles to support the Applicant's request for a biowaiver for the lower strength, MS8. Therefore, the BA waiver for MS8 is granted based on the comparative dissolution profiles of MS8 to that of MS16.

3. The proposed dissolution method is acceptable only on an interim basis, due to the following reason:

   - The proposed dissolution method is less than optimal. It does not follow USP's testing in "Acid Stage for 1 hour" and therefore it cannot be accepted as the final method. The accepted interim dissolution method on interim basis is as follows:

I. <u>Acid Stage:</u> **Apparatus:** **Speed:** **Medium:** **Time:**	**USP 1 (Basket)** **100 rpm** **Simulated gastric fluid 800 mL at 37ºC** **30 min (*as opposed to USP requirement, 60 min*)**
II. <u>Buffer Stage:</u> **Apparatus:** **Speed:** **Medium:** **Sampling times:**	**USP 2 (Paddle)** **100 rpm** **Fortified Intestinal Fluid 800 mL, at 37ºC** **10, 20, and 30 minutes**

4. The proposed dissolution acceptance criterion of Q= (b) (4) at 30 is not acceptable. A dissolution acceptance criterion of Q= (b) (4) at 30 min should be implemented on an interim basis, due to the following reason:

   - The dissolution data from the Pertzye capsule stability batches clearly show that the mean percent of lipase activity for MS8 and MS 16 is (b) (4) at 30 min; therefore, the proposed acceptance criterion of Q (b) (4) at 30 min is not appropriate. A dissolution criterion of Q= (b) (4) at 30 min is supported by the data and should be implemented on an interim basis until further data using the revised dissolution method are collected. The revised specifications table for this product with the updated dissolution interim criterion should be provided.

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5. ONDQA-Biopharmaceutics considers that the additional data supporting the setting of the final dissolution method and acceptance criterion can be submitted after the NDA's approval under a Post Marketing Commitment. The specific details of the PMC still need to be negotiated with the Applicant.

6. To support the approval of the final dissolution method and acceptance criterion the following should be provided:

   - For the setting of the final method, the Applicant should provide additional dissolution profile data (individual, mean, plots, n= 12) for both MS8 and MS16 strengths of the proposed Pertzye DR capsules. The testing should be conducted in acid stage for 1 hour and then the content should be transfer to the buffer stage for continuing testing using the proposed conditions.

   - For the setting of the final dissolution acceptance criterion of the Pertzye drug product, it is recommended that the Applicant collect additional dissolution profile data for lipase activity (using "Acid Stage – 1 hr"), from the batches manufactured during the first year after action date. The Applicant's proposal for the final dissolution acceptance criterion of the Pertzye drug product should be based on these data.

OVERALL ASSESSMENT

From the Biopharmaceutics perspective, the NDA 22-175 for Pertyze (pancrelipase) MS8 and MS16 DR capsules is acceptable with a post marketing commitment (PMC) if the applicant agrees. The following comments were conveyed to the Applicant on 04/20/12:

1. Your proposed dissolution method does not follow USP's testing in "Acid Stage for 1 hour" and it is less than optimal. Therefore, we consider that your proposed method is only acceptable on an interim basis. For the setting of the final method, you should provide additional dissolution profile data (individual, mean, plots, n= 12) for both M8 and M16 strengths of the proposed Pertzye DR capsules. The testing should be conducted in acid stage for 1 hour and then the content should be transfer to the buffer stage for continuing testing using the proposed conditions.

2. The dissolution data from the Pertzye capsule stability batches clearly show that the mean percent of lipase activity for MS16 is (b) (4) at 30 min and therefore, your proposed acceptance criterion of Q= (b) (4) at 30 min is not adequate. The provided data support a dissolution criterion of Q= (b) (4) at 30 min and it should be implemented. We consider that this implementation should be on an interim basis, until sufficient data using the revised dissolution method are available for the setting of the final criterion. Please provide the updated specifications table for this product with the revised interim dissolution criterion.

3. We consider that the additional data supporting the setting of the final dissolution method and acceptance criterion could be submitted after approval of your NDA

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under a Post Marketing Commitment. The specific details of the PMC can be discussed in a future teleconference.

_____	_____04/20/12_____
Tien-Mien Chen, Ph.D. Reviewer ONDQA Biopharmaceutics	Date

_____	_____04/20/12_____
Angelica Dorantes, Ph.D. Biopharmaceutics Supervisory Lead (acting) ONDQA Biopharmaceutics	Date

CC: DARRTS/ Resubmission NDA 22-175

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PRODUCT QUALITY - BIOPHARMACEUTICS ASSESSMENT

BACKGROUND

Pancrelipase is a complex mixture of enzymes with lipolytic, amylolytic, and proteolytic activities. The active ingredient, pancrelipase, is monographed in the USP. Pancrelipase is an enzyme therapy for the treatment of steatorrhea secondary to PEI, in disorders such as cystic fibrosis or chronic pancreatitis.

On 10/27/08, DCI submitted original NDA 22-175 for Pertzye (pancrelipase) DR capsule, (b) (4) 8,000 (MS8), and 16,000 (MS16) lipase units/capsules. It is a solid oral dosage form comprised of clear, gelatin capsules containing small enteric-coated microspheres of buffered pancreatic enzymes (lipase, amylase, and protease). For Pertzye, the pancreatic enzymes are isolated and concentrated from porcine pancreatic glands.

In the original submission, only the highest 16,000 lipase unit-strength was tested clinically. For the proposed (b) (4) 8,000 lipase unit-strengths, the Applicant employed (b) (4) On 08/27/09, FDA issued a CR letter for this NDA.

DCI responded and resubmitted the NDA on 02/15/10. In this resubmission, it was agreed upon between DCI and the Agency that DCI proposed (b) (4) The (b) (4) microspheres are filled into clear, hard gelatin capsules of different sizes. (b) (4) DCI received a second CR letter on 01/27/11. The submission history of this NDA is summarized by the Applicant as shown below.

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Table 1. The Submission History of Pertyze (Pancrelipase) DR Capsules

Date	Action
October 27, 2008	**DCI NDA#22-175 Submitted**
6/29-7/3, 7/6-10, 7/13-17 and 7/22/2009 (FDA483 presented on 7/22/2009)	FDA [redacted] (b) (4) District Office Inspection of DCI – PAI for NDA#22-175 and GMP
8/5, 9/30, 10/28, 11/27 and 12/30/2009	DCI Letters to [redacted] (b) (4) District: Response to 7/22/2009 Form FDA483
August 27, 2009	FDA issued an action letter representing the completion of the first review cycle for NDA#22-175
April 2010	In accordance with the Agency mandate to all manufacturers of unapproved Exocrine Pancreatic Insufficiency Drug Products, DCI ceased distribution of its Pancrelipase Delayed-Release Capsules (PANCRECARB®) because the NDA#22-175 had not achieved approval by that time.
July 29, 2010	DCI submitted a complete response to the Agency's August 27, 2009 NDA action letter. The rate limiting factor surrounding the timing of this response was related to the development and implementation of an HPLC analytical method.
10/29, 11/3,4,8-10,16-18,22,23, 12/6-9,13,14,20/2010 (FDA483 presented on 12/20/2010)	FDA [redacted] (b) (4) District Office conducted a second pre-approval inspection (PAI) at the DCI facility
January 7, 2011	DCI Letter to [redacted] (b) (4) Response to 12/20/2010 Form FDA483
January 27, 2011	FDA issued an action letter representing the completion of the second review cycle for NDA#22-175

Please see the ONQDA/Biopharmaceutics reviews for the two previous review cycles for details (*Reviews by Dr. Bogdan Kurtyka on 07/22/09 and by Dr. Tien-Mien Chen dated 12/09/10 in DARRTS*).

CURRENT SUBMISSION

After receiving a second CR letter dated 01/27/11, DCI requested a Type A meeting with the Agency on 05/02/11 and the meeting was held between DCI and the Agency on 06/22/11. DCI later resubmitted the NDA on 11/15/11. In this resubmission, the Applicant decided to pursue [redacted] (b) (4) Pertyze MS8 and MS16 DR capsules.

BIOPHARMACEUTICS REVIEW

During the third review cycle, a Biopharmaceutics Information Request was further sent to the Applicant on 01/20/12 and DCI responded on 02/07/12. A teleconference was held on 02/22/12. Additional Biopharmaceutics Information Requests were further sent to DCI on 02/23/12 and 03/30/12. DCI responded on 03/07/12 and 04/10/12, respectively. The Applicant's responses to the Agency's requests are reviewed here.

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FORMULATION COMPARISONS

The lipase activity is reportedly pH-dependent and optimal at pH 8-9. The 8,000 lipase unit strengths (MS8) are [redacted] (b) (4) to that of the 16,000 lipase unit strength (MS16) as shown below.

Table 2. Composition of Microsphere Formulation of Pertzye (Pancrelipase) DR Capsules

INGREDIENTS	Function	mg/Capsule		%w/w
		MS-8	MS-16	MS-8 and MS-16
Pancrelipase, USP [redacted] (b) (4) -1206	Active Ingredient	[redacted] (b) (4)		[redacted] (b) (4)
[redacted] (b) (4) -1208				
Sodium Carbonate [redacted] (b) (4) NF	[redacted] (b) (4)			
Sodium Bicarbonate, USP				
Sodium Starch Glycolate, NF				
Ursodiol, USP				
Polyvinylpyrrolidone, USP				
Cellulose Acetate Phthalate, NF				
Diethyl Phthalate, NF				
Talc, USP				
[redacted] (b) (4)				
TOTAL MASS				100%

[a] = [redacted] (b) (4)

[b] = Adjusted based on lipase activity

The microspheres of enteric-coated pancreatic enzymes are filled into clear, hard gelatin capsules of different sizes to make two different strengths, 8,000 and 16,000 IU lipase/capsule. The active ingredients of Pertzye DR capsules are shown below.

Table 3. The Active Ingredients of Pertzye (Lipase, Amylase, and Protease) DR Capsules

Name of Active Ingredients		Label Claim Unit Quantity (USP Units/ Capsule)	
Dosage Strength (DCI Internal Code Designation)		MS-8	MS-16
Pancrelipase, USP	Lipase	8,000	16,000
	Amylase	[redacted] (b) (4)	
	Protease		

Table 4. Label Claim Based on Lipase:Amylase and Lipase:Protease Ratios in Clinical Lot No. 6K09B

	Lipase Activity (USP Units/Cap)	Amylase Activity (USP Units/Cap)	Protease Activity (USP Units/Cap)	Label Claim for Amylase and Protease (average of Amylase and Protease activity, rounded down to nearest thousands)
MS-16 Clinical Lot 6K09B Actual Enzyme Content	[redacted] (b) (4)			
MS-8 Content Calculated Based on Clinical Lot Ratio				

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DISSOLUTION METHODOLOGY AND ACCEPTANCE CRITERION

The sponsor reported that a modified USP <711> test method (No. TM-6007) has been utilized to assess dissolution at 37ºC throughout the history of testing. The gastric exposure time is reduced to 30 minutes (from 60 minutes in acid stage as requested by USP method). The dissolution method is summarized below.

I. Acid Stage:

Apparatus: **1 (Basket) x 100 rpm**
Medium: **Simulated gastric fluid 800 mL**
Time: **30 min (as opposed to USP requirement, 60 min)**

II. Buffer stage:

Apparatus: **2 (Paddle) x 100 rpm**
Medium: **Fortified Intestinal Fluid 800 mL, at 37ºC**
Sampling: **10, 20, and 30 min**

(b) (4)

In the buffer stage, a small portion of dissolution medium was collected at certain times for assay of lipase release (% dissolved) at 37ºC. The % of lipase dissolved/released at 30 min in the buffer stage only accounted for (b) (4) of the labeled lipase activity (potency) for all the (b) (4) strengths. The acceptance criterion initially proposed was NLT (b) (4) (Q) at 30 minutes.

Whereas for determination of potency (lipase activity), a method (No. TM-6013) similar to the USP method was employed which was performed in (b) (4) The labeled activity (potency) of (b) (4) to (b) (4) was obtained at month "Zero".

The Biopharmaceutics Team concluded that

- The sponsor's proposed dissolution methodology is considered not optimal,
- The proposed specification of Q= (b) (4) at 30 min is considered less than ideal therefore,
- The biowaiver for the lower strength(s) could not be granted.

Several Biopharmaceutics comments were included in the second CR letter dated 01/27/11.

In this 3rd review cycle,

- A Biopharmaceutics information request was conveyed to the Applicant on 01/20/12 and DCI responded on 02/07/12 trying to solve the issue on the low recovery of lipase in dissolution testing

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- On 02/17/12, another information request was sent to the Applicant and the Applicant responded on 02/21/12 for discussion on the correction factor for the lipase activity calculation.
- On 02/22/12, a teleconference was held between the Applicant and the Agency for further discussion on recalculation of the lipase activity (using a mean correction factor) and resubmission of the recalculated data for 16,000 IU lipase units/capsule (clinical and stability batches) and 8,000 IU lipase units/capsule (stability batches only).
- On 03/07/12, DCI responded to the Biopharmaceutics information request dated 02/23/12 and resubmitted the revised lipase activity release using a mean correction factor (1.34).
- On 04/10/12, DCI further responded to the Biopharmaceutics information request dated 03/30/12 on the missing comparative dissolution profile of MS8 vs. that of MS16 to support the biowaiver for the MS8 capsules.

The Applicant's responses are reviewed and found acceptable. These responses are summarized below.

- The fortification components (with substrates added) in the dissolution buffer medium employed by the DCI (Method No. TM-6007) may not affect the complete recovery of the enzyme activities during dissolution testing. This is demonstrated by (b) (4) recovery of two other ingredients, amylase and protease upon dissolution at 30 min.

- The Total Lipase Activity Assay (Method No. TM-6013) is performed on (b) (4) which differs from the conditions experienced in the dissolution test (i.e., 37°C in dissolution medium) using their dissolution method No. TM-6007.

- The Applicant reported that the enteric-coated microsphere is designed to release enzyme product at the pH of the dissolution medium around pH 6.0. It is considered appropriate.

- USP allows for the use of correction factor for activity in phosphate buffer at 37°C, however, DCI has not historically employed the USP correction factor. DCI later obtained a mean correction factor (1.34) for lipase from 11 NDA stability lots as shown below.

- FDA and the Applicant agreed that the mean correction factor (1.34) will be adopted and used to recalculate the % dissolved/release of lipase activity during the dissolution testing at 30 min.

The mean correction factor was obtained from 11 stability batches as shown below.

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Table 5. Mean Correction Factor Obtained from 11 Stability Batches

	Column A	Column B	Column A divided by Column B
Stability Lot Number	**Total Lipase Activity USP Units/mg (TM-6013)**	**Dissolution Lipase USP Units/mg (TM-6007)**	**Factor**
9J27B-MS8	(b) (4)		
9J30B-MS8			
9L33B-MS8			
9A01B-MS8			
9L36B-MS16			
9L37B-MS16			
9L38B-MS16			
6H05B-MS16			
6K09B-MS16			
7A01B-MS16			
8H16B-MS16			
MEAN	**32.3**	**24.2**	**1.34**
STD DEV	**1.50**	**1.17**	**0.05**

- A correction factor may not be needed for protease or amylase activity. These enzymes are more stable, and considered not to be as sensitive to pH, media or temperature effects as the lipase.

- The mean value (1.34) of the correction factor would be adopted and used to recalculate the % dissolved/release of lipase activity during the dissolution testing.

- The Applicant would resubmit the recalculated % of lipase release in the dissolution testing and proposed the acceptance criterion at 30 min.

- Finally, the applicant submitted the comparative dissolution profiles between MS8 and MS16 to support the biowaiver for the lower strength MS8 which was not tested clinically.

The recalculated lipase activity obtained from the dissolution testing for Pertzye MS16 DR capsules (before and after using the correction factor 1.34) are tabulated below.

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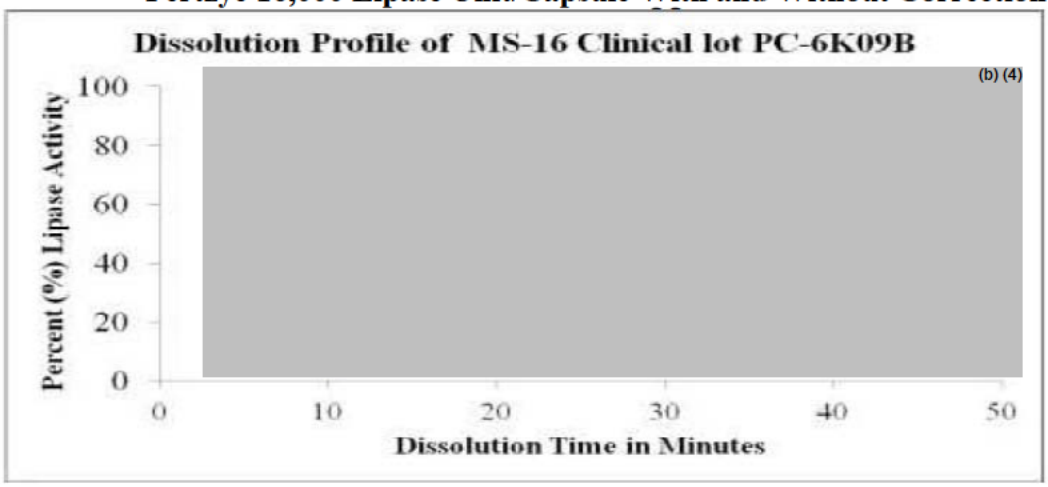
Table 6. The Corrected Lipase Activity and % Dissolved at 30 min Obtained from Clinical Batch (No. 6K09B) of Pertzye 16,000 Lipase Units/Capsule (n=6).

Column	A	B	C
Time in Min	Dissolution Lipase Activity (USP U/mg)	% Released (Dissolution Activity/Total Activity*)	*Corrected* % Released (Dissolution Activity/Total Activity**)
10	(b) (4)		
20			
30			
40			

*Column A divided by the Total Lipase Activity of 36.3 USP U/mg x 100
**Column B multiplied by correction factor of 1.34

Figure 1. Mean Dissolution Profile of Lipase for Clinical Lot (No. 6K09B) of Pertzye 16,000 Lipase Unit/Capsule With and Without Correction



The mean % of dissolved/release lipase activities obtained from the clinical and stability batches of MS16 after re-calculation using the mean correction factor (1.34) are shown below.

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Table 7. Stability Data Summary of MS-16 Capsules (16,000 IU Lipase Units/Capsule)

	Pull Dates (months) -->	0	3	6	9	12	18	24	30
LIPASE ACTIVITY (USP units / mg) (b) (4) of Total LIPASE Activity at Time = 0	Lot # PC-6H05B (Prot. # 070219)								(b) (4)
	Lot # PC-6K09B (Prot. # 070207)								
	Lot # PC-7A01B (Prot. # 070403)								
	Lot # PC-8H16B (Prot. # 090107)								
	Lot # PC-9L36B (Prot. # 091130)								
	Lot # PC-9L37B (Prot. # 091130)								
	Lot # PC-9L38B (Prot. # 091130)								
DISSOLUTION (USP units / mg) (b) (4) (Q) of Total LIPASE Activity at Time = 0	Lot # PC-6H05B (Prot. # 070219)								
	Lot # PC-6K09B (Prot. # 070207)								
	Lot # PC-7A01B (Prot. # 070403)								
	Lot # PC-8H16B (Prot. # 090107)								
	Lot # PC-9L36B (Prot. # 091130)								
	Lot # PC-9L37B (Prot. # 091130)								
	Lot # PC-9L38B (Prot. # 091130)								
AMYLASE ACTIVITY (USP units / mg) (b) (4) of Total AMYLASE Activity at Time = 0	Lot # PC-6H05B (Prot. # 070219)								
	Lot # PC-6K09B (Prot. # 070207)								
	Lot # PC-7A01B (Prot. # 070403)								
	Lot # PC-8H16B (Prot. # 090107)								
	Lot # PC-9L36B (Prot. # 091130)								
	Lot # PC-9L37B (Prot. # 091130)								
	Lot # PC-9L38B (Prot. # 091130)								
PROTEASE ACTIVITY (USP units / mg) (b) (4) of Total PROTEASE Activity at Time = 0	Lot # PC-6H05B (Prot. # 070219)								
	Lot # PC-6K09B (Prot. # 070207)								
	Lot # PC-7A01B (Prot. # 070403)								
	Lot # PC-8H16B (Prot. # 090107)								
	Lot # PC-9L36B (Prot. # 091130)								
	Lot # PC-9L37B (Prot. # 091130)								
	Lot # PC-9L38B (Prot. # 091130)								

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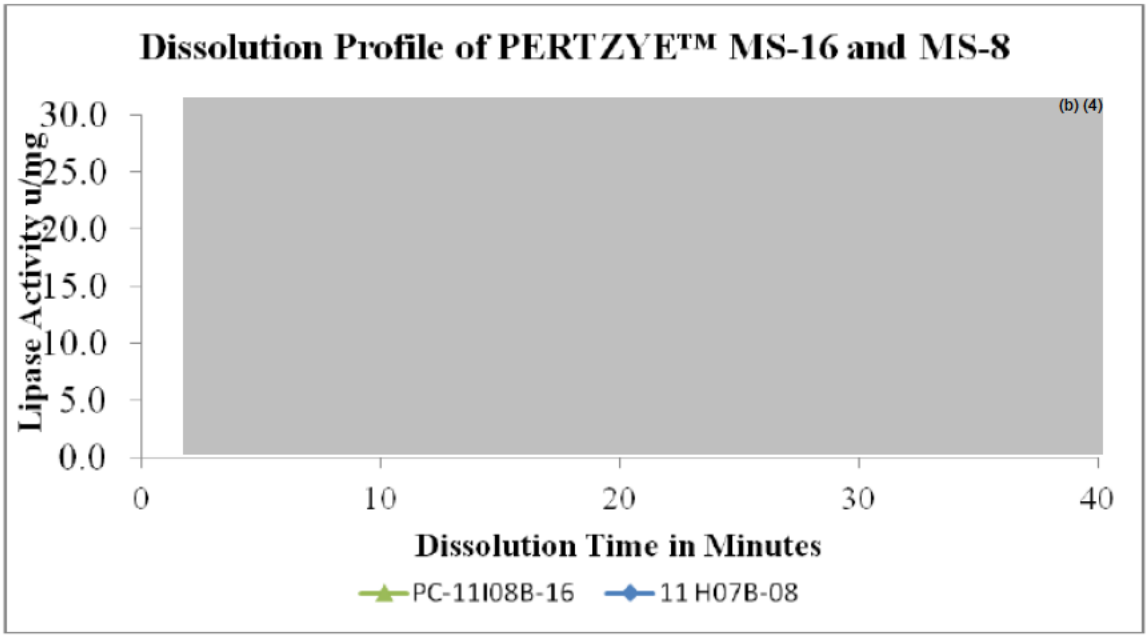
Mean comparative dissolution profiles between Pertyze MS8 and MS16 were submitted and shown below.

Table 8. Mean Comparative Dissolution Data of Lipase between Pertyze MS16 and MS8 DR Capsules

MS-16 Dissolution Profile (USP Units/mg)			
Lot #	10 min	20 min	30 min
PC-11I08B-16	(b) (4)		
Average (Mean)			
STDEV			

MS-8 Dissolution Profile (USP Units/mg)			
Lot #	10 min	20 min	30 min
11H07B-08	(b) (4)		
Average (Mean)			
STDEV			

Figure 2. Mean Comparative Dissolution Profiles of Lipase between Pertyze MS16 and MS8 DR Capsules



After recalculation using the mean correction factor (1.34), the mean % dissolution/release for the MS8 are 7% (at 10 min), 105% (at 20 min), and 105% (at 30 min) and those for MS16 are 30% (at 10 min), 102% (at 20 min), and 100% (at 30 min). The f2 value however, could not calculated, but both strength showed (b) (4) dissolved in 30 min similarly.

The mean percent of dissolved/release lipase activities obtained from the stability batches of MS8 after re-calculation using the mean correction factor (1.34) are shown below.

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Table 9. Stability Data Summary of MS-8 Capsules (8,000 IU Lipase Units/Capsule)

	Pull Dates (months) -->	0	3	6	9	12	18	24	30
LIPASE ACTIVITY (USP units / mg) (b) (4) of Total LIPASE Activity at Time = 0	Lot # PC-9A01B (Prot. # 090109)								(b) (4)
	Lot # PC-9J27B (Prot. # 091130)								
	Lot # PC-9J30B (Prot. # 091130)								
	Lot # PC-9L33B (Prot. # 091130)								
DISSOLUTION (USP units / mg) (b) (4) (Q) of Total LIPASE Activity at Time = 0	Lot # PC-9A01B (Prot. # 090109)								
	Lot # PC-9J27B (Prot. # 091130)								
	Lot # PC-9J30B (Prot. # 091130)								
	Lot # PC-9L33B (Prot. # 091130)								
AMYLASE ACTIVITY (USP units / mg) (b) (4) of Total AMYLASE Activity at Time = 0	Lot # PC-9A01B (Prot. # 090109)								
	Lot # PC-9J27B (Prot. # 091130)								
	Lot # PC-9J30B (Prot. # 091130)								
	Lot # PC-9L33B (Prot. # 091130)								
PROTEASE ACTIVITY (USP units / mg) (b) (4) of Total PROTEASE Activity at Time = 0	Lot # PC-9A01B (Prot. # 090109)								
	Lot # PC-9J27B (Prot. # 091130)								
	Lot # PC-9J30B (Prot. # 091130)								
	Lot # PC-9L33B (Prot. # 091130)								

Reviewer's Comments:

1. Based on the clinical lot (No. 6K09B) and the stability lots of MS16 and MS8, Pertzye DR capsules showed (b) (4) dissolved/release of lipase at 30 min at the time of manufacturing (Time Zero). Therefore, the Applicant's proposed dissolution acceptance criterion needs to be (b) (4) from Q= (b) (4) at 30 min to Q= (b) (4) at 30 min.

2. Based on the comparative dissolution profiles and data between Pertyze MS16 and MS8 DR capsules, the biowaiver for the lower strength MS8 which has not been tested clinically could be granted.

3. A PMC is need for a new dissolution method (following the USP, i.e., Acid stage for 1 hour and then transfer the content to Buffer stage.

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Resubmission of NDA 22-175/N-000 for Pertzye (Pancrelipase) DR Capsules, (b) (4) 8,000, and 16,000 Lipase Units/Capsule

Appendix 1

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Lipase Activity Calculation and Comparative Dissolution Data between MS8 and MS16 Capsules

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/s/

TIEN MIEN CHEN
04/21/2012

ANGELICA DORANTES
04/22/2012

CLINICAL PHARMACOLOGY REVIEW

NDA	**22-175**
Drug Name	**PERTZYE™ (pancrelipase)**
Description of Submission	**Resubmission**
Submission Date	**11/18/11**
Date Received	**11/18/11**
Review Type	**Priority (6 months)**
Primary Reviewer	**Dionna Green, M.D.**
Team Leader	**Yow-Ming Wang, Ph.D.**
OCP Division	**DCP 3**
OND Division	**DGIEP**
Sponsor	**Digestive Care, Inc.**
Formulation(s); Strength(s)	**Delayed-release capsules;** **MS-8 (8,000 USP units of lipase/28,750 USP units of protease/30,250 USP units of amylase)** **MS-16 (16,000 USP units of lipase/57,500 USP units of protease/60,500 USP units of amylase)**
Proposed Indication	**Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions**

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1 EXECUTIVE SUMMARY

PERTZYE (pancrelipase delayed-released capsules) is a pancreatic enzyme product containing enteric-coated microspheres of buffered lipase, amylase, and protease and is intended for the treatment of exocrine pancreatic insufficiency (EPI) due to cystic fibrosis or other conditions. This is the third review cycle for this new drug application (NDA), which was originally submitted on October 27, 2008 and has since received two Complete Response (CR) actions from the Division due to multiple deficiencies related to product quality, facility inspections, and assay methodologies.

In this current submission, the Applicant has submitted a complete response to the most recent Complete Response letter dated January 27, 2011. This letter listed nine deficiencies, one of which was related to clinical pharmacology. Clinical pharmacology deficiency #8 stated the following:

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

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

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

To address this deficiency, the Applicant has submitted two reports. The first, TMV-050, is a test method validation report intended to verify that the test method (TM-6013) for lipase activity is suitable for determining lipase activity of the PERTZYE enteric-coated microspheres when exposed to applesauce. The objective of this study was to demonstrate the precision and accuracy of the TM-6013 method in this setting. The second report, RR-231, is a comprehensive applesauce compatibility study intended to demonstrate lipase stability for PERTZYE microspheres when exposed to applesauce at room temperature for 20 minutes.

1.1 Recommendation

The Office of Clinical Pharmacology has reviewed the clinical pharmacology information submitted in the resubmission of NDA 22-175 and agrees that the Applicant's response to address Clinical Pharmacology deficiency #8 is sufficient and that the data provided support the

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approval of PERTZYE (pancrelipase) delayed-release capsules for the treatment of exocrine pancreatic insufficiency.

1.2 Phase IV Commitments

None

1.3 Summary of Key Clinical Pharmacology and Biopharmaceutics Findings

Background
The current submission represents the third review cycle for NDA 22-175 for PERTZYE (pancrelipase) Delayed-Release Capsules. This product has undergone two previous review cycles, both of which received CR actions due to multiple deficiencies.

PERTZYE Delayed-Release Capsules are orally administered capsules that contain enteric-coated (EC) microspheres of buffered pancreatic enzymes (lipase, amylase, and protease). The active pharmaceutical ingredient (API) is pancrelipase, USP and is isolated and concentrated from swine pancreas. The microspheres are covered with (b) (4) enteric coating. The coating is intended to minimize destruction or inactivation of the product in gastric acid. PERTZYE is designed to release most of the enzymes in vivo at pH greater than 5.5. Pancreatic enzymes are not systemically absorbed from the gastrointestinal tract in appreciable amounts.

The capsules are typically swallowed with liquids at the start of each meal. For specific patient populations, such as pediatrics, swallowing the capsule may be difficult; therefore opening the capsules and sprinkling the microspheres onto a soft acidic food such as applesauce can provide an alternative method of administration. The drug product capsules will be manufactured in 2 strengths, MS-8 (8,000 USP units of lipase/28,750 USP units of protease/30,250 USP units of amylase) and MS-16 (16,000 USP units of lipase/57,500 USP units of protease/60,500 USP units of amylase). (b) (4) Therefore, the use of PERTZYE in pediatric patients 1 month to less than 12 months of age and weighing less than 8 kg and patients greater than 4 years of age weighing less than 16 kg will be limited by the available dosage strengths and their ability to provide the recommended dose based on age and weight. Attempting to divide the capsule contents into small fractions to deliver small doses of lipase is not recommended. The Division recommends that the dosing provided for PERTZYE be based on age and minimum weight (see Pediatric and Maternal Health Staff [PMHS] consult dated 02/27/12).

The proposed dosing for PERTZYE is as follows:

Children Older than 12 Months and Younger than 4 Years and Weight 8 kg or Greater
Dosing should begin with 1,000 lipase units/kg of body weight per meal for children less than age 4 years to a maximum of 2,500 lipase units/kg of body weight per meal (or less than or equal to 10,000 lipase units/kg of body weight per day), or less than 4,000 lipase units/g fat ingested per day.

Children 4 Years and Older and Weight 16 kg or Greater and Adults

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Dosing should begin with 500 lipase units/kg of body weight per meal for those older than 4 years to a maximum of 2,500 lipase units/kg of body weight per meal (or less than or equal to 10,000 lipase units/kg of body weight per day), or less than 4,000 lipase units/g fat ingested per day.

Usually, half of the prescribed PERTZYE dose for an individualized full meal should be given with each snack. The total daily dose should reflect approximately three meals plus two or three snacks per day.

Regulatory History

Review Cycle #1

The Applicant, Digestive Care, Inc., originally filed NDA 22-175 on October 27, 2008. PeiFan Bai, Ph.D. completed the clinical pharmacology review for the original submission (see review by Dr. Bai dated June 9, 2009). The studies reviewed by Dr. Bai and her conclusions are described below:

In Vivo Intubation Study (Bioavailability Study):

This was an open-label, placebo-controlled, crossover study that evaluated the bioavailability of PERTZYE in seven patients with EPI. Five capsules of PERTZYE MS-16 or placebo were taken with the Lundh test meal (a liquid test meal containing protein, fat, and sugar); gastric and duodenal aspirates were collected to determine the bioavailability of lipase, amylase, and protease. Based on the clinical pharmacology reviewer's calculation after taking into account the lipase activity recovered following placebo, there appears to be only a small amount of % lipase activity (<10%) recovered following PERTZYE. The reviewer commented that clogging of catheters might have influenced the outcome of duodenal lipase recoveries. The clinical pharmacology reviewer noted that the bioavailability study using the intubation procedure is considered unreliable for assessing the *in vivo* delivery of pancreatic enzymes to the duodenum. The bioavailability study is not a required study for the NDA approval.

In Vitro Stability Study (Applesauce Compatibility Study):

The percentages of lipase activities recovered after mixing with applesauce were determined for each of the three (b) (4) dosage strength formulations. The results are listed below.

Mean (SD) % lipase activities after exposure to applesauce at room temperature are shown in **Table 1** below.

Table 1 – Mean (SD) % Lipase Activities After Exposure to Applesauce at Room Temperature

	Dosage Strength Formulations		
	MS-4	MS-8	MS-16
Exposure Duration	40 minutes	60 minutes	50 minutes
Lipase activity	90% (3.5%)	91% (3.8%)	93% (3.6%)

(Table above modified from table in Dr. Bai's Clinical Pharmacology Review dated June 9, 2009.)

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Upon initial review, Dr. Bai concluded the following: (a) Based on the above results for individual strengths, the lipase activities recovered after mixing with applesauce were higher than the current standard of at least 90%. (b) PERTZYE EC microspheres, MS-4, MS-8 and MS-16, were stable after exposure to applesauce at room temperature for 40 min, 60 min, and 50 min, respectively. (c) The study results support the use of applesauce as a medium to facilitate ingestion of PERTZYE EC microspheres.

Dr. Bai revised the assessment of the *in vitro* stability study (see Dr. Bai's Addendum to Clinical Pharmacology Review dated August 26, 2009) after the CMC reviewer had identified a product deficiency (see Item #10 of Deficiency Items in CR letter dated) related to the pancrelipase assay method and measurement of lipase activity. Dr. Bai's final recommendation was for the Applicant to repeat the *in vitro* stability study using the analytical method described in Deficiency Item #10 (i.e., use of a minimum of 5 data points for determination of assay linearity rather than (b)(4) data points) but otherwise the same study design as that submitted.

In the first review cycle, ultimately a CR action was the recommendation by the Clinical Pharmacology discipline. In addition to CMC Deficiency Item #10 listed under product quality, a second deficiency item (Deficiency Item #19) was noted by clinical pharmacology:

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

In addition to this, the initial submission had multiple other deficiencies involving product quality, clinical data, and REMS. Therefore, the Division issued a CR letter listing a total of 21 deficiencies on August 27, 2009 and requested the Applicant address the deficiencies prior to the approval of the product.

Review Cycle #2

The Applicant resubmitted the NDA on July 29, 2010 to start a new review cycle. Although the resubmission was not considered to be a complete response for other review disciplines, it included reviewable clinical pharmacology information in response to Deficiency #19 stated above. Jang-Ik Lee, Pharm.D., Ph.D. completed the clinical pharmacology review of validations reports for lipase (TMV-047) and protease (TMV-043) assay methods and an applesauce compatibility report (RR-166). Dr. Lee concluded that the validation reports were not acceptable to fulfill Clinical Pharmacology Deficiency Item #19 in the CR letter dated August 27, 2009. Although the Applicant addressed the issue of constructing a calibration curve for the lipase assay (CMC Deficiency Item #10), the Applicant did not determine the accuracy and precision of the assay by simultaneously running quality control (QC) samples to verify in-process lipase assay performance. He also concluded that the applesauce compatibility study report submitted to demonstrate the compatibility of the proposed product when mixed with applesauce was not considered to be in complete form. A CR action was the recommendation by the Clinical Pharmacology discipline and the following deficiency (Deficiency Item #8a and b) and recommendation were communicated to the Applicant:

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

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

In addition to this, this resubmission had multiple other deficiencies related to product quality and inadequate facilities inspection. Therefore a CR action was taken by the Division and a letter detailing a total of 9 deficiencies was issued on January 27, 2011.

Current Review Cycle
The Applicant resubmitted the NDA on November 18, 2011 to start a third review cycle. This resubmission provides response to the CR letter dated January 27, 2011. To address Deficiency Item #8 related to clinical pharmacology, the Applicant has submitted two reports, TMV-050 and RR-231.

Clinical Pharmacology Findings

Test Method Validation
TMV-050 is a test method validation study report intended to verify that the test method (TM-6013) for lipase activity is suitable for determining lipase activity of the PERTZYE enteric-coated microspheres when exposed to applesauce. The objective of this study was to demonstrate the precision and accuracy of the TM-6013 method for the determination of lipase activity in this setting. Additionally, quality control samples to check in-process assay performance were to be run simultaneously.

The accuracy was determined by running the assays in duplicate at six concentrations of the assay range (6, 8, 10, 12, 14, and 16 U/mL). The accuracy was 92-107% for the QC samples (unexposed microspheres) and 98-102% for the microspheres exposed to 5mL of applesauce for 20 minutes. These results met the pre-specified acceptance criteria of an accuracy of 85-115% in accordance with the protocol. The precision of the method was determined by running the assays in duplicate at six concentrations (6, 8, 10, 12, 14 and 16 U/mL) over a period of three days. The precision ranged from 1.4-2.5% CV for the concentrations tested for the QC Samples and 0.9-3.5% CV for the microspheres exposed to 5 mL of applesauce. All results for precision met the acceptance criteria of Relative Standard Deviation (RSD) less than 15% in accordance with the protocol. The results for accuracy and precision confirm the suitability of the test method for its intended use.

In vitro Stability Study (Applesauce Compatibility Study)

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RR-231 is a comprehensive applesauce compatibility study intended to demonstrate lipase stability vs. time based on % total lipase, when the PERTZYE EC microspheres are exposed to applesauce.

This study also evaluated the performance of the applesauce exposed microspheres on dissolution. This data was reviewed by the Product Quality Reviewer (see Quality review authored by Dr. Howard Anderson).

At least three product batches were to be tested. The % of total lipase activity remaining after the microspheres are exposed to the applesauce for 20 minutes was calculated as total lipase activity after 20 minutes exposure divided by percent label claim of drug product times 100. The mean lipase activity for each of the three lots ranged from 96-99%. All three lots met the acceptance criteria in accordance with the protocol (the % of total lipase activity remaining after the microsphere are exposed to the applesauce 20 minutes should not be less than 90% of the label claim). The comparative % lipase activity recovered after the 20 minutes exposure to applesauce at room temperature was also determined as compared to the QC samples. The mean % recovery of lipase activity after 20 minutes of exposure to applesauce ranges from 97-98%. The results of the study confirmed the stability of PERTZYE microspheres exposed to applesauce for at room temperature for 20 minutes.

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2 QUESTION-BASED REVIEW (ABBREVIATED)

1. Is the lipase assay method acceptable to determine the lipase activity of the microspheres when the product is mixed with applesauce?

Yes, the assay method is acceptable to determine the lipase activity of microspheres when the product is mixed with applesauce. The lipase activity of PERTZYE enteric-coated microspheres exposed to applesauce was determined using a previously validated enzymatic assay (TMV-047). This method measures lipase activity (U/mg) in a reaction mixture containing 2 mL of 80 mg/mL sodium taurocholate solution, 8 mL of buffer solution, 9 mL DW, 10 mL olive oil substrate, 0.1 NaOH, and 1 mL of the enzyme solution. Titration plots of 0.1 NaOH consumed versus time are constructed and used to calculate lipase activity as follows:

Lipase activity (U/mg) = mL NaOH/min * N NaOH * 1000) / mg sample assayed

As documented in TMV-050, the assay demonstrates acceptable intra-day accuracy (98% to 102%) and inter-day precision (0.9% to 3.5% CV) when applied to applesauce-exposed PERTZYE EC microspheres. Additionally, the inter-day accuracy for the applesauce-exposed microsphere was estimated to be 98-105%.

2. Is the compatibility data acceptable for the administration of PERTZYE after mixed with applesauce?

Yes, the compatibility data is acceptable for the administration of PERTZYE EC microspheres after mixed with applesauce. Study report RR-231 details the lipase stability when PERTZYE EC microspheres were exposed to applesauce at room temperature for up to 20 minutes. The % label claim based on total lipase activity ranged from 96-99%, meaning all three lots met the acceptance criteria in accordance with the protocol (the % of total lipase activity remaining after the microsphere are exposed to the applesauce 20 minutes should not be less than 90% of the label claim). The mean comparative % lipase activity recovered (QC Samples vs. microspheres exposed to applesauce) was acceptable, ranging from 97-98%.

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3 DETAILED LABELING RECOMMENDATIONS

Agency proposed labeling revisions are: addition (blue and underlined) and deletion (~~red and strikethrough~~) as shown below:

(b) (4)

2 pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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4 INDIVIDUAL STUDY REVIEW

4.1 Individual Study Review

4.1.1 TMV-050

Title
"Determination of Lipase Activity of the Applesauce Exposed PERTZYE Enteric-Coated Microspheres"

Objective
To demonstrate the precision and accuracy of the TM-6013 method for determination of lipase activity in PERTZYE EC microspheres recovered after exposure to applesauce.

Reviewer Comment:
Test method TM-6013 has been previously validated in TMV-047 by evaluating the specificity, accuracy, and precision, linearity, and range for the analysis of PERTYZE EC microspheres that have not been exposed to applesauce. Therefore, the scope of TMV-050 is limited to the objective stated above.

Materials
- Test Material
  - PERTZYE enteric-coated microspheres
  - Applesauce (GERBER, 2-3.5 oz. pack baby food)
  - Pancreatin Lipase Reference Standard, USP
- Reagents and Solutions
  - All reagents and solutions were prepared in accordance with DCI TM-6013 "Determination of Lipase Activity in Digestive Enzyme Preparations"

Methods
Accuracy: The intra-day accuracy of the method was determined by running the assays in duplicate at six concentrations of the assay range (6, 8, 10, 12, 14 and 16 U/mL).
Precision: The inter-day precision of the method was determined by running the assays in duplicate at six concentrations (6, 8, 10, 12, 14 and 16 U/mL) over a period of three days.

Acceptance Criteria
- Accuracy (% Recovery): Average lipase activity recovery from the applesauce is 85-115%. Recovery experiments will be performed by comparing lipase activity of the recovered microspheres after washing off the applesauce with distilled water to the unexposed EC microspheres (QC samples). At least 67% (4 out of 6) of QC samples should be within 15% of their respective nominal value, 33% of the QC samples (not all replicates at the same concentration) may be outside 15% of nominal value.
- Precision: Relative Standard Deviation (RSD) is less than 15%, for inter-day precision, determined over a period of three days, (6 Concentrations, 2 replicates each).

Results

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As displayed in **Table 2** and **Table 3** below, the accuracy was 92-107% for the QC Samples (Unexposed Microspheres) and 98-102% for the microspheres exposed to 5mL of applesauce for 20 minutes, respectively. All results for accuracy met the acceptance criteria in accordance with the protocol.

Table 2 – Intra-day Accuracy (QC Samples)

Concentration	mL of 0.1N NaOH Consumed	Lipase Activity USP units/mg		Calculated Mean (Lipase Activity For Rep #1 and Rep #2) USP U/mg	% Accuracy*	Pass/Fail (85-115%)
		Replicate #1	Replicate #2			
6 U/mL	0.313	32.66	30.93	31.8	107	Pass
8 U/mL	0.381	30.46	30.37	30.4	102	Pass
10 U/mL	0.482	29.12	29.71	29.4	99	Pass
12 U/mL	0.563	29.25	28.92	29.1	98	Pass
14 U/mL	0.633	27.94	27.65	27.8	93	Pass
16 U/mL	0.706	27.28	27.39	27.3	92	Pass

*Accuracy = (Calculated Mean / Actual Lipase Activity) x 100
29.8 USP U/mg

Table 3 – Intra-day Accuracy (Microspheres Exposed to 5 mL of Applesauce)

Concentration	Lipase Activity USP units/mg		Calculated Mean (Lipase Activity) Rep #1 and Rep #2) USP U/mg	Accuracy** (% Recovery)	Pass/Fail
	Replicate #1	Replicate #2			
6 U/mL	32.36	32.49	32.4	102	Pass
8 U/mL	30.46	29.21	29.8	98	Pass
10 U/mL	29.64	28.76	29.2	99	Pass
12 U/mL	29.55	29.67	29.6	102	Pass
14 U/mL	27.61	26.78	27.2	98	Pass
16 U/mL	27.46	27.64	27.5	101	Pass

**Accuracy = (Lipase Activity of applesauce exposed EC microspheres/ Lipase Activity of the EC microspheres without exposure) x 100

As displayed in **Table 4** and **Table 5** below, the precision ranged from 1.4-2.5% for the concentrations tested for the QC Samples and 0.9%-3.5% for the microspheres exposed to 5 mL of applesauce, respectively. All results for precision met the acceptance criteria in accordance with the protocol.

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Table 4 – Inter-day Precision (QC Samples)

Concentration	6 U/mL	8 U/mL	10 U/mL	12 U/mL	14 U/mL	16 U/mL
	Lipase Activity (USP U/mg)					
Day 1, Replicate 1	32.66	30.46	29.12	29.25	27.94	27.28
Day 1, Replicate 2	30.93	30.37	29.71	28.92	27.65	27.39
Day 2, Replicate 1	32.98	30.24	30.23	28.93	27.50	27.61
Day 2, Replicate 2	31.97	31.01	29.77	30.52	28.21	28.35
Day 3, Replicate 1	33.23	32.20	29.85	29.50	27.63	27.91
Day 3, Replicate 2	32.54	31.13	30.78	28.94	28.65	27.45
Mean	32.4	30.9	29.9	29.3	27.9	27.7
SD	0.83	0.73	0.56	0.62	0.44	0.40
RSD	2.5%	2.4%	1.9%	2.1%	1.6%	1.4%
Pass/Fail	Pass	Pass	Pass	Pass	Pass	Pass

Table 5 – Inter-day Precision (Microspheres Exposed to 5 mL Applesauce)

Concentration	6 U/mL	8 U/mL	10 U/mL	12 U/mL	14 U/mL	16 U/mL
	Lipase Activity (USP U/mg)					
Day 1, Replicate 1	32.36	30.46	29.64	29.55	27.61	27.46
Day 1, Replicate 2	32.49	29.21	28.76	29.67	26.78	27.64
Day 2, Replicate 1	32.61	30.25	30.91	29.52	27.60	27.08
Day 2, Replicate 2	32.18	30.93	29.94	29.50	27.63	26.67
Day 3, Replicate 1	32.57	31.84	30.54	30.23	29.09	28.19
Day 3, Replicate 2	34.15	32.13	30.76	29.57	28.68	27.66
Mean	32.7	30.8	30.1	29.7	27.9	27.5
SD	0.71	1.08	0.82	0.28	0.84	0.52
RSD	2.2%	3.5%	2.7%	0.9%	3.0%	1.9%
Pass/Fail	Pass	Pass	Pass	Pass	Pass	Pass

<u>Reviewer Comment:</u>
Report TMV-050 describes a partial validation intended to verify that the already validated test method (TM-6013 as documented in TMV-047) is suitable for determining the activity of PERTZYE EC microspheres when exposed to a different matrix (e.g., 5 mL applesauce for 20 minutes). In this report, the Applicant has determined the intra-day accuracy and the inter-day precision for the method, which were acceptable. Inter-day accuracy and intra-day precision were not calculated and reported by the Applicant; however, utilizing the available data provided in the validation report this Reviewer was able to calculate the inter-day accuracy. The intra-day precision was not estimated for each concentration level because only two replicated were available. Utilizing the calculated mean derived from the replicate data at each of the six concentrations over a three-day period, the inter-day accuracy reported as % recovery is 98-105% for the microspheres exposed to applesauce (

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Table 6*). This validation report confirms that the test method is verified and suitable for its intended use.*

Table 6 – Inter-day Accuracy (Microspheres Exposed to 5 mL of Applesauce)[a]

Concentration	6 U/mL	8 U/mL	10 U/mL	12 U/mL	14 U/mL	16 U/mL
Lipase Activity (USP U/mg)						
Day 1, Replicate 1	32.36	30.46	29.64	29.55	27.61	27.46
Day 1, Replicate 2	32.49	29.21	28.76	29.67	26.78	27.64
Day 2, Replicate 1	32.61	30.25	30.91	29.52	27.60	27.08
Day 2, Replicate 2	32.18	30.93	29.94	29.50	27.63	26.67
Day 3, Replicate 1	32.57	31.84	30.54	30.23	29.09	28.19
Day 3, Replicate 2	34.15	32.13	30.76	29.57	28.68	27.66
Day 1 Mean	32.43	29.84	29.20	29.61	27.20	27.55
Day 2 Mean	32.40	30.59	30.42	29.51	27.62	26.88
Day 3 Mean	33.36	31.99	30.65	29.90	28.89	27.93
Reference Value*	31.8	30.4	29.4	29.1	27.8	27.3
Day 1 Accuracy	**102%**	**98%**	**99%**	**102%**	**98%**	**101%**
Day 2 Accuracy	**102%**	**101%**	**103%**	**101%**	**99%**	**98%**
Day 3 Accuracy	**105%**	**105%**	**104%**	**103%**	**104%**	**102%**

*Calculated mean lipase activity for QC samples (see Table 2)
a Independent Analysis

Conclusion

The report demonstrates the accuracy and precision of the TM-6013 method for the intended use of determination of lipase activity of the microspheres recovered from the applesauce matrix.

4.1.2 RR-231

Title

"Lipase Stability of the PERTYZE Enteric Coated Microspheres when Exposed to Applesauce"

Objective

Reference ID: 3120202

To determine the lipase stability of EC microspheres when exposed to applesauce at room temperature for 20 minutes.

Reviewer's Comment:
This study also evaluated the performance of the applesauce exposed microspheres on dissolution. This data was reviewed by the Product Quality Reviewer (see Quality review authored by Dr. Howard Anderson).

Materials

- Test Material
  - PERTZYE MS-16 (16,000 USP Units of Lipase/Capsule) EC microspheres – 3 lots of drug product:
    - Lot PC – 11H06B-16-01
    - Lot PC – 11H07B-16-01
    - Lot PC – 11I08B-16-01
  - Applesauce (GERBER – baby food, 5oz. packs)
- Reagents and Solutions
  - Reagents and preparation of solutions for lipase activity assay were in accordance with DCI TM-6013, Determination of Lipase Activity in Digestive Enzyme Preparations.

Methods
The applesauce used in the study was measured for pH at the initiation of the study to verify its acidity. Three lots of finished product as QC Samples (unexposed to applesauce), were assayed for total lipase activity (lipase potency) in accordance with test method TM-6013.

Stability in Applesauce (% of label claim based on total lipase activity after exposure to applesauce): The stability of the EC microspheres in applesauce was determined by placing 5 mL of applesauce in a specimen cup and pouring two opened capsules of PERTZYE MS-16 (approximately 1,093 mg of EC microspheres) into the cup. The microspheres in the applesauce were mixed using a flat end spatula. The mixture was allowed to stand for 20 minutes at room temperature. The contents were then poured into a 500 mL glass beaker with the assistance of a few mL of distilled water. A minimum of 200 mL of distilled water was added to the beaker so that the applesauce came off the microspheres and the microspheres settled at the bottom of beaker. The washing was decanted carefully without losing the microspheres. The total time of washing, decanting and recovery of the microspheres did not exceed 5 minutes. The recovered microspheres were ground in cold distilled water using a mortar and pestle. The ground microspheres were transferred quantitatively to a 500 mL volumetric flask with the aid of cold distilled water and diluted to the final volume of 500 mL. During the testing, the stock solution was kept in an ice-water bath and continuously stirred. From the cold stock solution, 15 mL was transferred (by pipette) into a 100 mL volumetric flask and cold distilled water added to the final volume of 100 mL. The solution was mixed using a stir bar and maintained in ice water bath. The solution was immediately assayed for its lipase activity in accordance with test method TM-6013.

Acceptance Criteria

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The % of total lipase activity remaining after the microspheres are exposed to the applesauce for 20 minutes should not be less than 90% of the label claim. [Example: 28.3 USP u/mg x 549 mg/capsule / 16000 u/capsule x 100]

Results

All three lots met the acceptance criteria in accordance with the study protocol (RP-231) demonstrating the PERTZYE EC microspheres are stable in applesauce for 20 minutes at room temperature based on the % total lipase activity.

The % of total lipase activity remaining after the microspheres are exposed to the applesauce for 20 minutes was calculated using the following calculation:

% of label claim based on total lipase activity	=	(Total lipase activity after 20 minute exposure to applesauce x capsule fill weight / percent label claim of drug product) x 100

The results for the QC samples and the microsphere exposed to applesauce are shown in **Table 7** below:

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Table 7 – % of Label Claim Based on Total Lipase Activity

Sample Number	QC Sample Lipase Activity (USP u/mg)	QC Sample %Lipase Activity	After 20 Min. Applesauce Exposure Lipase Activity (USP u/mg)	After 20 Min. Applesauce Exposure % Lipase Activity
MS-16 Lot PC-11H06B-16-01 (Capsule Fill Weight = 549mg)				
1	29.6	102%	28.3	97%
2	29.4	101%	30.1	104%
3	29.2	100%	28.1	97%
Mean	29.4	101%	28.8	99%
STDEV	0.2	NA	1.1	NA
%RSD	0.7	NA	3.8	NA
MS-16 Lot PC-11H07B-16-01 (Capsule Fill Weight = 542mg)				
1	30.6	102%	30.0	100%
2	30.7	102%	30.7	102%
3	30.8	103%	28.7	96%
Mean	30.7	102%	29.8	99%
STDEV	0.1	NA	1.0	NA
%RSD	0.3	NA	3.4	NA
MS-16 Lot PC-11I08B-16-01 (Capsule Fill Weight = 549mg)				
1	30.6	99%	29.5	95%
2	31.0	100%	29.6	96%
3	30.7	99%	30.2	97%
Mean	30.8	99%	29.8	96%
STDEV	0.2	NA	0.4	NA
%RSD	0.7	NA	1.3	NA

The comparative % lipase activity recovered after the 20 minutes exposure to applesauce at room temperature was also determined as compared to the QC Samples using the following calculation:

Comparative % of total lipase activity	=	(Total lipase activity of the applesauce exposed microspheres/ Total lipase activity of the QC microsphere without applesauce exposure) x 100

Results are shown in **Table 8** below:

Table 8 – Comparative % Lipase Activity Recovered

Reference ID: 3120202

Sample Number	QC Sample Lipase Activity (USP u/mg)	After 20 Min. Applesauce Exposure Lipase Activity (USP u/mg)	After 20 Min. Applesauce Exposure Comparative % Lipase Activity Recovered
MS-16 Lot PC-11H06B-16-01			
1	29.6	28.3	96%
2	29.4	30.1	102%
3	29.2	28.1	96%
Mean	29.4	28.8	98%
STDEV	0.2	1.1	n/a
%RSD	0.7	3.8	n/a
MS-16 Lot PC-11H07B-16-01			
1	30.6	30.0	98%
2	30.7	30.7	100%
3	30.8	28.7	93%
Mean	30.7	29.8	97%
STDEV	0.1	1.0	n/a
%RSD	0.3	3.4	n/a
MS-16 Lot PC-11I08B-16-01			
1	30.6	29.5	96%
2	31.0	29.6	96%
3	30.7	30.2	98%
Mean	30.8	29.8	97%
STDEV	0.2	0.4	n/a
%RSD	0.7	1.3	n/a

Conclusion

The results of the study confirm the stability of the PERTZYE EC microspheres when exposed to applesauce at room temperature for 20 minutes.

Reviewer's Comment:

The results from this stability study support the following labeling claim: "For patients who are unable to swallow intact capsules, the capsules may be carefully opened and contents mixed with small amounts of acidic soft food with a pH of 4.5 or less (e.g., applesauce)."

Reference ID: 3120202

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/s/

DIONNA J GREEN
04/20/2012

YOW-MING C WANG
04/20/2012

CLINICAL PHARMACOLOGY REVIEW

NDA	**22-175 SN 30**
Drug Name	**Pertzye® (pancrealipase)**
Description of Submission	**Resubmissions**
Letter Date	**7/29/10**
Date Received	**7/30/10**
Primary Reviewer	**Jang-Ik Lee, Pharm.D., Ph.D.**
Team Leader (Acting)	**Gilbert J. Burckart, Pharm.D.**
OCP Division	**DCP 3**
OND Division	**DGIP**
Sponsors	**Digestive Care, Inc.**
Formulation	**Capsules containing enteric-coated microspheres, (b) (4) MS-8, and MS-16**
Proposed Indication	**1. Treatment of exocrine pancreatic insufficiency (b) (4)**

Pertzye (pancrelipase) Delayed-Release Capsules, Buffered and Enteric-Coated Microspheres contain lipase, amylase, and protease. The enzyme-containing microspheres are covered with a (b) (4) enteric coating. The active pharmaceutical ingredient (API) is pancrelipase, USP. Pancrelipase is isolated and concentrated from swine pancreas.

The Applicant, Digestive Care, Inc. initially submitted this NDA on October 27, 2008. PeiFan Bai, Ph.D. completed the clinical pharmacology review of the first submission (see the review logged in DARRTS on June 9, 2009). In the first submission review, she concluded that the NDA is acceptable for approval from a clinical pharmacology standpoint. However, she amended the review on February 18, 2010 due to the deficiency in the pancrelipase assay method recognized by the CMC review team (CMC Deficiency #10 in the fisrst complete response letter).

The initial submission has multiple deficiencies on product quality, clinical pharmacology, clinical and REMS. Therefore, the Agency issued a complete response letter with 21 deficiencies on August 27, 2009 and requested to address the deficiencies for the approval of the proposed product. The clinical pharmacology deficiency and recommendation were:

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

product administration will be labeled based on the results of the repeat study, if found acceptable.

The Applicant resubmitted the NDA on February 17, 2010. Although the resubmission was not considered to be complete for other discipline reviews, it includes reviewable clinical pharmacology information in response to Deficiency #19 stated above. The applicant submitted complete resubmission on July 29, 2010 to start a new review cycle.

Recently, the Office of Compliance found multiple serious issues and GMP violations with the drug substance manufacturer, (b) (4) and enter a withhold approval recommendation. The major issue is that both FDA field laboratories and CFSAN laboratories have analyzed samples of pancrelipase drug substance manufactured by (b) (4) for the presence of *Bacillus cereus* diarrheal enterotoxin in several batches. A warning letter (FDA Form 483) to (b) (4) is expected to be issued soon and an early action may be taken by issuing another complete response letter to the applicant.

CLINICAL PHARMACOLOGY RECOMMENDATION

The Applicant's response to address Clinical Pharmacology Deficiency #19 is not acceptable. Although the Applicant addressed the issue on constructing calibration curve for lipase assay (CMC Deficiency #10), the Applicant did not determine the accuracy and precision of the assay by simultaneously running quality control (QC) samples to check in-process lipase assay performance. In addition, the study report submitted to demonstrate the compatibility of the proposed product when mixed with apple sauce is not a complete one for a sufficient clinical pharmacology review. Therefore, the reviewer recommends the Applicant submit an adequate assay validation report with the assessment of in-process assay performance, and a complete food compatibility study report for a substantial clinical pharmacology review. Otherwise, the statements instructing the administration of the product by mixing apple sauce needs to be removed from the proposed labeling.

CLINICAL PHARMACOLOGY REQUEST TO BE CONVEYED TO THE APPLICANT

The validation reports for lipase (TMV-047) and protease (TMV-043) assay methods submitted on February 15, 2010 are not acceptable to fulfill Clinical Pharmacology Deficiency # 19 in the complete response letter dated August 27, 2009. Furthermore, the applesauce compatibility study report (RR-166) submitted simultaneously is not considered to be a complete form. We recommend you include in-process assay performance during actual study sample runs by simultaneously running quality control samples in the validation reports. In order to prepare for adequate assay performance report, we refer you to Section C. Application to Routine Drug Analysis in the current Guidance for Industry (Page 17): Bioanalytical Method Validation. (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf). We also recommend you submit a comprehensive apple sauce compatibility report for our substantial clinical pharmacology review. For example, the methods section needs to include the detailed information in a degree that an independent laboratory can reproduce the same results. At least 3 product batches need to be tested for each product strength.

QUESTION-BASED REVIEW

1. Is the improved pancrelipase assay method acceptable to determine the product compatibility when the drug product is mixed with apple sauce?

No, the improved assay method is not acceptable to determine the product compatibility. Although the Applicant addressed the issue on constructing calibration curves for lipase and protease assay methods (CMC Deficiency #10), the Applicant did not determine the accuracy and precision of the assay methods by simultaneously running quality control (QC) samples to check in-process pancrelipase assay performance.

As recommended in CMC Deficiency #10, the linearity of the calibration curves was assessed by performing a statistical evaluation of the regression line through five lipase (Report TMV-047: 8, 10, 12, 14 and 16 USP U/mL) and protease concentration points (Report TMV-043: 2.5, 3.1, 3.7, 4.3 and 5.0 USP U/mL) in triplicate, which yielded a correlation coefficient (r) of 0.992 and 0.996 respectively.

However, the specificity, accuracy and precision of the assay methods were determined using the same triplicate calibration curve samples. Furthermore, the in-process assay performance during actual study sample runs has not been determined. In addition, the validation of calibration curves was conducted only once so that between-assay variabilities have not been reported.

2. Is the compatibility data acceptable for the administration of Pertzye after mixed with apple sauce?

No, the compatibility data submitted by the Applicant is not sufficient to determine whether it is compatible to mix the proposed product with apple sauce. The Applicant did not adequately validate the pancrealipase assay methods and submit the in-process assay performance as described in Question 1 above. Furthermore, the compatibility study report (RR-166) submitted by the Applicant is not the one that can be substantially reviewed. For example, Materials and Methods section contains only two short sentences so that the reviewer cannot evaluate whether the Applicant used acceptable methods to determine the compatibility or not. Results section includes % lipase activity determined 20 and 30 minutes after apple sauce exposure for 3 samples in 2 batches of highest product strength (i.e., MS-16) only. The report does not include the compatibility data on protease activity.

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/s/

JANG IK LEE
01/11/2011

GILBERT J BURCKART
01/13/2011

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	22-175
Submission Date:	02/15/10 (Response to CR Letter), 03/31/10, and 07/29/10 (Resubmission)
Brand Name:	Pertzye
Generic Name:	Pancrelipase
Formulation:	Delayed release (DR) capsule
Strength:	16,000, 8,000, and 4,000 lipase units/capsules
Sponsor:	Digestive Care Inc. (DCI)
Type of submission:	Original (N-000)
Reviewer:	Tien-Mien Chen, Ph.D.

SUMMARY

Pancrelipase is a complex mixture of enzymes with lipolytic, amylolytic, and proteolytic activities. The active ingredient, pancrelipase, is monographed in the USP. Pancrelipase is an enzyme therapy for the treatment of steatorrhea secondary to pancreatic enzyme insufficiency (PEI), in disorders such as cystic fibrosis or chronic pancreatitis. Pancrelipase is acid labile, so most of the PEPs (pancreatic enzyme products) contain pancrelipase in enteric-coated minitablets, microspheres, or granules within the capsules for oral administration. Pancrelipase are not materially absorbed by the gastrointestinal tract

PEPs were developed before the Food and Drug Administration (FDA) approval requirements for NDAs enacted in 1938. Since 2004, upon request by the Agency, several NDAs for PEPs have been submitted and have been reviewed and approved. DCI's pancrelipase capsules (named Pancrecarb) are also on the US market for the treatment of PEI without FDA approval.

On 10/27/08, DCI submitted NDA 22-175 for Pertzye (pancrelipase) DR capsule, (b) (4) 8,000, and 16,000 lipase units/capsules. For Pertzye, the pancreatic enzymes are isolated and concentrated from porcine pancreatic glands. Pertzye (pancrelipase) capsules are a solid oral dosage form comprised of clear, gelatin capsules containing small enteric-coated microspheres of buffered pancreatic enzymes.

In the original submission, the sponsor employed (b) (4) DCI received a complete response (CR) letter dated 08/27/09. DCI responded to the CR letter on 02/15/10 and resubmitted the NDA on 07/29/10.

In this resubmission, it was agreed upon between DCI and the Agency that DCI proposed (b) (4) However, only the 16,000 lipase units/cap was tested clinically. Dissolution testing/data for the (b) (4) proposed strengths, plus the developed dissolution methodology and the proposed specification were also submitted and therefore, reviewed here.

The dissolution results showed that at month "Zero", the mean % of lipase dissolved at 30 min only accounted for (b) (4) of the labeled lipase activity (potency) for all the (b) (4) strengths whereas, the labeled activity (potency) of (b) (4) was obtained. The sponsor did not fully justify the loss of the activity during the dissolution testing.

RECOMMENDATION

From the Biopharmaceutics perspective, the sponsor's proposed dissolution methodology is considered not optimal and the proposed specification of Q= (b) (4) at 30 min is considered less than ideal therefore, they are not acceptable and the biowaiver for the (b) (4) lower strengths could not be granted at this time.

The sponsor needs to address the following Agency's information request appropriately. The following comments need to be conveyed to the sponsor.

COMMENTS (Need to be sent to the sponsor)

1. You responded on 03/31/10 to the Agency's request on 03/22/10 for further exploration and/or explanation for the causes of the loss of the activity during the dissolution testing. You indicated that 1). You already explored various conditions (under study report No. RR-083) and 2). The Agency, in a letter dated 05/07/09, already accepted the sponsor proposed dissolution specifications Q= (b) (4) at 30 min.

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

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

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

2. Please consider conducting dissolution testing using the USP dissolution method, i.e., in the acid stage for 1 hour and then transfer the content to the buffer stage.

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

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

BACKGROUND

Pancrelipase is a complex mixture of enzymes with lipolytic, amylolytic, and proteolytic activities. The active ingredient, pancrelipase, is monographed in the USP. Pancrelipase is an enzyme therapy for the treatment of steatorrhea secondary to PEI, in disorders such as cystic fibrosis or chronic pancreatitis.

Pancrelipase is acid labile, so most of the PEPs contain enteric-coated pancrelipase minitablets, microspheres, or granules within the capsules for oral administration. Pancreatic enzymes are not materially absorbed by the gastrointestinal tract.

PEPs were developed before the FDA approval requirements for NDAs enacted in 1938. Since 2004, upon request by the Agency, several NDAs for PEPs had been submitted and have been reviewed and approved. DCI's pancrelipase capsules (named Pancrecarb) are also on the US market for the treatment of PEI without FDA approval.

CURRENT SUBMISSION

On 10/27/08, DCI submitted NDA 22-175/N-000 for Pertzye (pancrelipase) DR capsule, (b) (4) 8,000, and 16,000 lipase units/capsules. It is a solid oral dosage form comprised of clear, gelatin capsules containing small enteric-coated microspheres of buffered pancreatic enzymes (lipase, amylase, and protease). For Pertzye, the pancreatic enzymes are isolated and concentrated from porcine pancreatic glands.

In the original submission, the sponsor employed (b) (4) DCI received a CR letter dated 08/27/09. DCI responded and resubmitted the NDA on 02/15/10. In this resubmission, it was agreed upon between DCI and the Agency that DCI proposed (b) (4) Dissolution testing/data for the (b) (4) proposed strengths, plus the developed dissolution methodology and proposed specification were also submitted and therefore, reviewed here.

FORMULATION COMPARISONS

The sponsor reported that the enzyme-containing microspheres are coated with (b) (4) enteric coating to provide protection against gastric inactivation of the buffered enzymes during gastric passage. The inclusion of the sodium carbonate/sodium bicarbonate-buffer excipients in the formulation (b) (4)

Pancreatic enzymes are variable in their hydrophobicity and water solubility. (b) (4) ursodiol is included in the formulation as (b) (4) The lipase activity is reportedly pH-dependent and optimal at pH 8-9.

The (b) (4) 8,000 lipase unit strengths are (b) (4) to that of the 16,000 lipase unit strength as shown below. The microspheres are filled into clear, hard gelatin capsules of different sizes.

Table 1-1. The Composition and Formulation of Pertzye (pancrelipase) DR Capsules

INGREDIENTS	Function	mg/Capsule		% w/w	
		MS-8	MS-16	MS-8	MS-16
Pancrelipase, USP (b) (4)-1206	Active Ingredient	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)-1208					
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)					
Clear Hard Gelatin Capsules (b) (4)					
Ink	Printing on capsules	Blue [b]	Red [b]	Blue [b]	Red [b]
TOTAL MASS		(b) (4)		**100.0**	**100.0**

[a] = (b) (4)

[b] = Trace amounts

[c] = Adjusted based on lipase activity

Table 1-2. The Active Ingredients of Pertzye (Lipase, Amylase, and Protease) DR Capsules

Name of ingredients		Unit Quantity (USP Unit/ capsule)		
	Dosage Strength	(b) (4)	MS-8	MS-16
Pancrelipase, USP	Lipase		8,000	16,000
	Amylase		(b) (4)	
	Protease			

DISSOLUTION METHODOLOGY AND SPECIFICATIONS

The sponsor reported that a modified USP <711> test method (TM-6007) has been utilized to assess dissolution throughout the history of testing. The gastric exposure time is reduced to 30 minutes (from 60 minutes as requested by USP method) with an acceptance criterion of NLT (b) (4) (Q) in 30 minutes and the dissolution media employs fortified intestinal juice as summarized below.

I. Acid Stage:
Apparatus: 1 (basket) x 100 rpm
Medium: Simulated gastric fluid 800 mL
Time: 30 min (as opposed to USP requirement, 60 min)

II. Buffer stage:
Apparatus: 2 (paddle) x 100 rpm
Medium: Fortified Intestinal Fluid 800 mL*

Sampling: 10, 20, and 30 min
Specification: Q= (b) (4) in 30 min

*. The preparation of the fortified intestinal fluid:

(b) (4)

Lipase is an enzyme which catalyses the hydrolysis of emulsified triglycerides (olive oil as the substrate) into free fatty acids, glycerol, and fatty acyl glycerides at a water-lipid interface. One USP unit of lipase activity is contained in the amount of pancrelipase that liberates 1.0 µEq. of acid per minute at pH 9.0 and 37°C under the conditions of the Assay for lipase activity. Please see the calculation of USP lipase unit in Appendix 1 for details.

Determination of lipase activity in digestive enzyme preparation for dissolution testing employed a test method (No. TM-6013) which was reported to be similar to the USP method. The lipase activity obtained from the dissolution testing for the Pertzye DR capsules are tabulated below.

Table 2. Lipase Activity and % Dissolved at 30 min Obtained from Three Stability Batches (up to 30 months) of Pertzye 16,000 Lipase Unit Capsules.

LIPASE ACTIVITY (% Label Claim)								
Lot	*0 mos*	*3 mos*	*6 mos*	*9 mos*	*12 mos*	*18 mos*	*24 mos*	*30 mos*
PC-6K09B	(b) (4)							
PC-6H05B								
PC-7A01B								
AMYLASE ACTIVITY (% Label Claim)								
PC-6K09B	(b) (4)							
PC-6H05B								
PC-7A01B								
PROTEASE ACTIVITY (% Label Claim)								
PC-6K09B	(b) (4)							
PC-6H05B								
PC-7A01B								
DISSOLUTION (% Lipase Label Claim)								
PC-6K09B	(b) (4)							
PC-6H05B								
PC-7A01B								

Figure 1. The Stability Profile of Lipase for Three Stability Batches (up to 30 months) of Pertzye 16,000 Lipase Unit-Capsules

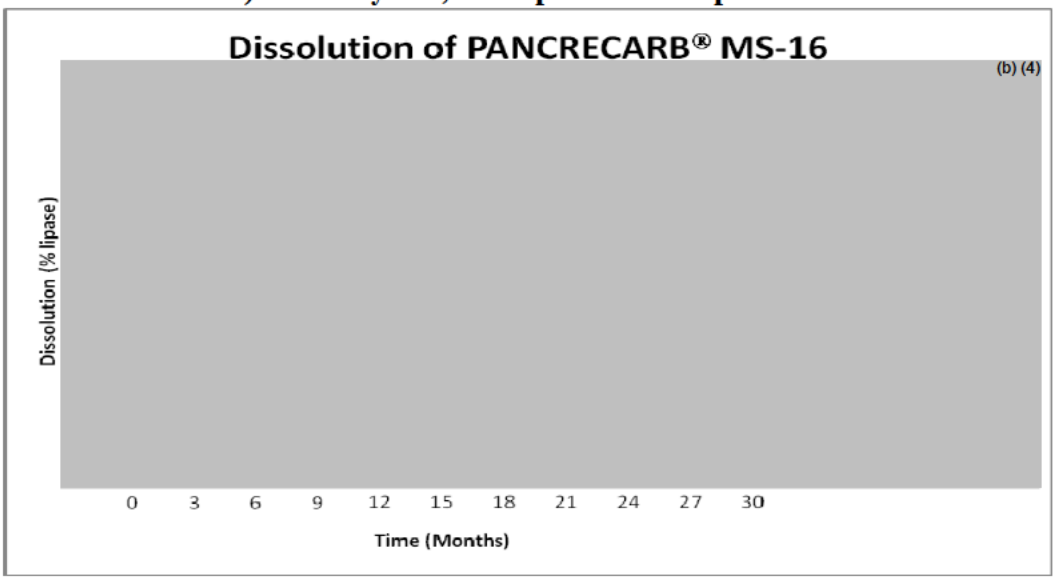

Table 3. Lipase Activity and % Dissolved at 30 min Obtained from One Stability Batch (up to 9 months) of Pertzye 8,000 Lipase Unit-Capsules.

LIPASE ACTIVITY (% Label Claim)								
Lot	*0 mos*	*3 mos*	*6 mos*	*9 mos*	*12 mos*	*18 mos*	*24 mos*	*30 mos*
PC-9A01B	(b) (4)							
AMYLASE ACTIVITY (% Label Claim)								
PC-9A01B	(b) (4)							
PROTEASE ACTIVITY (% Label Claim)								
PC-9A01B	(b) (4)							
DISSOLUTION (% Lipase Label Claim)								
PC-9A01B	(b) (4)							

(b) (4)

The % of lipase dissolved at 30 min in the buffer stage only accounted for (b) (4) of the labeled lipase activity (potency) for all the (b) (4) strengths whereas, the labeled activity (potency) of (b) (4) was obtained at month "Zero" (Tables 2-4).

The dissolution development report (No. 0906606) was submitted in the original submission. It was to explore the dissolution conditions (with respect to buffer pHs) and the loss of lipase activity, 1). In various or other enteric-coatings materials, 2), In various temperatures and time of gastric exposure, and 3). With and without substrates added in order to achieve maximum gastric stability and to preserve the lipase activity during dissolution testing. Please see the study report No. RR-083 for details.

Reviewer's Comments: (Need NOT be sent to the sponsor)

1. The sponsor's proposed dissolution specification of Q= (b) (4) at 30 min is considered not optimal. The sponsor responded on 03/29/10 to the Agency's request on 03/22/10 for further exploration and/or explanation for the causes of the loss of the activity during dissolution testing. The sponsor indicated that 1) They already explored various conditions (under study report No. RR-083) and 2). The Agency, in a letter dated 05/07/10, already accepted the sponsor proposed dissolution specifications Q= (b) (4) at 30 min.

   Based on the results of the study No. RR-083, the sponsor selected the fortified intestinal fluid as a medium for the dissolution testing in which substrates were added to stabilize the pancrelipase, i.e., olive oil for lipase, casein for protease, and starch for amylase. This reviewer would raise questions regarding 1). The sponsor's dissolution method (TM-6007) using the fortified intestinal fluid (in which olive oil was added to stabilize the lipase) and 2). The assay method (TM-6013) used for determining lipase activity in the dissolution fluid using olive oil again as a substrate for titration by 0.1 N NaOH solution.

   As stated in the assay procedure for lipase (TM-6013), dissolution samples were alkalized using 0.1 N NaOH to pH 9.2 and olive oil as a substrate was added. The 0.1 N NaOH was then used for titration to maintain the pH at 9.0. Thus, the appropriateness of using the method TM-6013 for lipase assay is questioned. The sponsor did not clarify whether the amount of olive oil added to the fortified intestinal fluid will later affect the determination of lipase activity when titrating the fatty acid liberated from the substrate, olive oil, after being digested by lipase. Therefore, the sponsor's proposed Q= (b) (4) at 30 min is not considered fully justified. The sponsor needs to justify the use of fortified intestinal fluid as a dissolution medium vs. the use of the USP lipase assay method.

2. There have been ongoing significant issues with the Pertzye drug substance manufacturer, (b) (4) These issues have led Compliance to enter a withhold approval recommendation into EER. (b) (4) A CR action on this NDA would be expected with a target action date in mid-December of this year. Therefore, the Biopharmaceutics

comments (p. 2) will be included in the CR letter for further justification of Q= (b) (4) at 30 min.

3. The biowaiver for the (b) (4) lower strengths, 8,000 (b) (4) lipase units/caps could not be granted at this time.

_____	_____12/08/10_____
Tien-Mien Chen, Ph.D. Reviewer ONDQA Biopharmaceutics	Date
_____	_____12/08/10_____
Patrick Marroum, Ph.D. ONDQA Biopharmaceutics	Date

CC: NDA
Patrick Marroum, Angelica Dorantes, Tien-Mien Chen

Resubmission of NDA 22-175/N-000 for Pertzye (Pancrelipase) DR Capsules, (b) (4) 8,000, and 16,000 Lipase Units/Capsule

Appendix 1

Lipase Activity Calculation:

(b) (4)

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/s/

TIEN MIEN CHEN
12/08/2010

PATRICK J MARROUM
12/09/2010

ADDENDUM to CLINICAL PHARMACOLOGY REVIEW

NDA: 22-175	Submission Date(s): Oct 27, 2008; March 13, 2009
Brand Name	Pancrecarb®
Generic Name	Pancrelipase
Reviewer	PeiFan Bai, Ph.D.
Secondary Reviewer	Jang-Ik Lee, Pharm. D., Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND division	Division of Gastroenterology Products
Sponsor	Digestive Care, Incorporated
Submission Type; Code	Original
Formulation; Strength(s)	Buffered and Enteric-coated microspheres (b) (4) MS-8, and MS-16
Indication	1. Treatment of exocrine pancreatic insufficiency (b) (4)

This addendum is to the original NDA review which was filed in DFS in May, 2009 and is concerning the analytical method used for the in-vitro applesauce stability study.

In the complete response letter to the sponsor, CMC comment # 10 states that "In regards to your analytical methodologies, we have the following comments:

a. The assessment of linearity for the lipase and protease assays is conducted using (b) data points. We recommend a minimum of 5 data points for determination of assay linearity.

b. Clarify your acceptance criteria for lipase assay linearity."

This addendum is to address the deficiency listed above which was not identified in our original NDA review.

For the lipase activity, the sponsor used (b) data points to establish the assay linearity. In its document entitled "Verification of USP Pancrelipase Method for Lipase Activity," the sponsor reported a correlation coefficient of 0.992 based on (b) (4) data points. This result is less satisfactory since the FDA recommends that 5 data points be used for the determination of assay linearity (Guidance for Industry: Analytical Method Validation, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf).

The reviewer concurs with the statement of CMC in the FDA's complete response letter regarding the requirement for 5 data points in establishing assay linearity. The submitted applesauce study (Protocol #080705) is deemed unacceptable since the assay method was not adequately validated. Therefore, we recommend that the sponsor repeat the applesauce study with a newly validated analytical method based on CMC's recommendation (a minimum of 5 data points for determination of assay linearity), and submit the results of the repeated applesauce study to FDA for review. The recommendation in the labeling with regard to the use of applesauce as a mixing medium to facilitate administration will be based on the review outcome. If the sponsor chooses not to repeat the applesauce stability study, there will be no recommendations with regard to the use of applesauce in the labeling.

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

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/s/

PEIFAN J BAI
08/26/2009

JANG IK LEE
08/26/2009
Secondary Reviewer's Correction

In the Guidance for Industry for Analytical Method Validation referred in this Addendum Review, FDA recommends at least 4 out of 6 non-zero standards should meet the listed criteria (see Page 6 of the Guidance for more information). Thus, the data points mentioned in the last sentence on the first page of this review should read ¿6 data points.¿

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 22-175	Submission Date(s): Oct 27, 2008; March 13, 2009
Brand Name	Pancrecarb®
Generic Name	Pancrelipase
Reviewer	PeiFan Bai, Ph.D.
Secondary Reviewer	Jang-Ik Lee, Pharm. D., Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND division	Division of Gastroenterology Products
Sponsor	Digestive Care, Incorporated
Submission Type; Code	Original
Formulation; Strength(s)	Buffered and Enteric-coated microspheres, (b) (4) MS-8, and MS-16
Indication	1. Treatment of exocrine pancreatic insufficiency (b) (4)

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1 Executive Summary

1.1 Recommendation

From the clinical pharmacology perspective, the application is considered approvable provided the labeling comments are adequately addressed by the sponsor.

1.2 Phase IV Commitments

No.

1.3 Regulatory Backgrounds

The Agency issued finalized guidelines for the New Drug Application requirements in April 2006. One requirement is demonstration of the bioactivity and/or bioavailability of the active ingredients at the site of action (gastrointestinal tract); i.e. lipase, amylase, and protease activities should be determined from aspirates from the stomach and duodenum.

On November 26, 2007, Fast Track designation was granted for PANCRECARB® for the treatment of exocrine pancreatic insufficiency. DCI subsequently submitted an amendment to IND#45223 (Serial No. 055) dated April 17, 2008 containing a request to submit portions of the NDA for review before the complete NDA is submitted (i.e., rolling submission).

1.4 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The product: PANCRECARB® (pancrelipase) Delayed-Release Capsules, Buffered and Enteric-Coated Microspheres contain lipase, amylase, and protease. Pancrelipase is isolated and concentrated from the pancreatic glands of pigs. The enzyme-containing microspheres are coated with [redacted] (b) (4) enteric coating.The Active Pharmaceutical Ingredient (API) is pancrelipase, USP. The sponsor proposed to market [redacted] (b) (4) MS-8 (lipase: 8,000 USP units), and MS-16 (lipase: 16,000 USP units).

The proposed dosing regimen: begin therapy with 1,000 USP units of lipase/kg of body weight/meal in children less than 4 years of age, and 500 lipase units/kg/meal [redacted] (b) (4) in children 4 years and older. Adjust dosage according to symptoms to less than 2,500 units/kg/meal [redacted] (b) (4) or less than 4,000 lipase units/g of fat per day.

In-vitro stability in applesauce study: The percentages of lipase activities recovered after mixing with applesauce were determined for all [redacted] (b) (4) strengths. The results are listed below.

Mean (SD%) lipase activities left after exposure to applesauce at room-temperature

strength	MS-4 (40 min exposure)	MS-8 (60-min exposure)	MS-16 (50-min exposure)
Lipase activity	90%(3.5%)	91% (3.8%)	93%(3.6%)

Based on the above results for individual strengths, the lipase activities recovered after mixing with applesauce were higher than the current standard of at least 90%. Pancrecarb® microspheres, MS-4, MS-8 and MS-16, were stable after exposure to

applesauce at room temperature for 40 min, 60 min, and 50 min, respectively. The study results support the use of applesauce as a medium to facilitate ingestion of PANCRECARB® microspheres.

In-vivo bioavailability study: The bioavailability of PANCRECARB® was completed in 7 exocrine pancreatic insufficient patients with an open label, placebo controlled, crossover study design. Five capsules of PANCRECARB® MS-16 were taken with the Lundh test meal in the active treatment phase. Five capsules of Placebo were taken with the Lundh test meal in the Placebo phase. Gastric and duodenal aspirates were collected during each phase to determine the bioavailability of lipase, amylase, and protease that were derived from exogenously administered PANCRECARB®. The sponsor used the total volume of standardized liquid Lundh test meal plus the volume of PEG perfused to calculate the volume correction factor and to estimate individual enzyme activities recovered. Though 2 mg/ml non-absorable PEG was used as the marker, the sponsor did not assay for PEG in duodenal aspirates to more accurately determine individual volume correction factors.

The Agency accepts the use of lipase bioavailability only to assess the in-vivo performance of pancreatic lipase products. With correction for individual enzyme baseline levels prior to dosing, the increased enzyme levels in the duodenal aspirates accounted for approximately 33% lipase, 40% amylase and 45% protease recovery, following ingestion of five capsules of PANCRECARB®. The sponsor did not calculate the % lipase recovered following placebo, which could have served as an approximate indicator of endogenous duodenal pancreatic enzyme secretion upon food ingestion. Based on the reviewer's calculation after taking into account the lipase activity recovered following placebo, there appears to be only small amount of % lipase activity (<10%) recovered following PANCRECARB®. Based on the results submitted, the bioavailability of PANCRECARB® appears to be low. Clogging of catheters might have influenced the outcome of duodenal lipase recoveries.

According to the ongoing internal discussions of DPG, the bioavailability study using the intubation procedure is considered unreliable for assessing the in-vivo delivery of pancreatic enzymes to the duodenum. According to a verbal communication with the clinical reviewer, Dr. Marjorie Dannis, the pivotal study demonstrated that PANCRECARB® is efficacious. Therefore, the sponsor may not need to repeat the bioavailability study. In response to our information request dated April 15, 2009, the sponsor submitted additional information on June 3, 2009 with regards to the bioavailability study. Since the bioavailability study with an intubation procedure is considered unreliable, the June-3-2009 submitted information is not reviewed.

2 Question Based Review

2.1 General Attributes

2.1.1 What are the components and composition of Pancrecarb® Liquid Concentrate?

PANCRECARB® (pancrelipase) Delayed-Release Capsules, Buffered and Enteric-Coated Microspheres contain lipase, amylase, and protease. Pancrelipase is isolated and concentrated from the pancreatic glands of pigs. The enzyme-containing

microspheres are coated with [redacted] (b) (4) enteric coating to provide protection against gastric inactivation of the buffered enzymes during gastric passage.

The Active Pharmaceutical Ingredient (API) is pancrelipase, USP. [redacted] (b) (4) strengths of pancrelipase are utilized in the production of PANCRECARB®: [redacted] (b) (4) Pancreatic Enzyme [redacted] (b) (4) 1208) [redacted] (b) (4)

[redacted] (b) (4)

Each PANCRECARB® MS-8 capsule contains:

Lipase - 8,000 USP Units

Amylase - [redacted] (b) (4)

Protease - [redacted]

Each PANCRECARB® MS-16 capsule contains:

Lipase - 16,000 USP Units

Amylase - [redacted] (b) (4)

Protease - [redacted]

The component and composition of the to-be-marketed formulation is summarized in Table 1 below.

Table 1. The component and composition of the to-be-marketed formulation

INGREDIENTS		mg/Capsule			% w/w			Function
		(b) (4)	MS-8	MS-16	(b) (4)	MS-8	MS-16	
Pancrelipase, USP	(b) (4) 1206			(b) (4)			(b) (4)	Active Ingredient
	(b) (4) 1208							
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 (b)						100.0	100.0	

** Adjusted based on lipase activity

Lipase consists of 449 amino acid residues in a single polypeptide chain; its complete amino acid sequence has been reported. Two isoenzymes of two isoenzymes have nearly identical amino acid compositions but differ slightly in their glycosylation patterns. The characrteristics of lipase are summarized in Table 2 below.

(b) (4)

[redacted]

(b) (4)

2.1.2 What is the proposed indication of Pancrecarb

Pancrecarb® capsules are proposed to treat exocrine pancreatic insufficiency (b) (4)

2.1.3 What is the proposed mechanism of action of Pancrecarb®?

Pancreatic lipase, one of the exocrine enzymes present in pancreatic secretion, breaks down triglycerides (fats) into free fatty acids, glycerol and fatty acyl glycerides. It is essential for the efficient digestion of dietary triglycerides. Amylase and proteases are digestive enzymes capable of breaking down carbohydrates and proteins, respectively.

2.1.4 What are the proposed dosage and route of administration?

Pancrecarb® capsules consist of buffered and enteric-coated microspheres, and are manufactured for oral administration. The sponsor proposes to market (b) (4) MS-8, and MS-16, where (b) (4) MS-8 8,000 Lipase units, and MS-16 16,000 Lipase units. The proposed dosing regimen is "begin therapy with 1,000 USP units of lipase/kg of body weight/meal in children less than 4 years of age 500 lipase units/kg/meal (b) (4) in children 4 years and older. Adjust dosage according to symptoms to less than 2,500 units/kg/meal (b) (4) or less than 4,000 lipase units/g of fat per day."

2.1.5 What is the regulatory background?

Regulatory requirement for pancreatic enzyme products:
The Agency issued the sponsor the finalized guidelines for the New Drug Application (NDA) requirements in April 2006. One requirement is demonstration of the bioactivity and/or bioavailability of the active ingredients at the site of action (gastrointestinal tract); i.e. lipase, amylase, and protease activities should be determined from aspirates from the stomach and duodenum.

On November 26, 2007, Fast Track designation was granted for PANCRECARB® for the treatment of exocrine pancreatic insufficiency. DCI subsequently submitted an amendment to IND#45223 (Serial No. 055) dated April 17, 2008 containing a request to submit portions of the NDA for review before the complete NDA is submitted (i.e., rolling submission).

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology studies used to support dosing?

The study was an open label, placebo controlled, crossover study of the bioavailability of PANCRECARB® performed in exocrine pancreatic insufficient patients. Gastric and duodenal aspirates were collected to determine the bioavailability of lipase, amylase, and protease that were derived from exogenously administered PANCRECARB®.

After the 30-minute baseline samples were obtained, each subject swallowed 5 capsules of the placebo with a standardized liquid 500 mL Lundh test meal. The liquid Lundh meal consisted of skimmed milk powder mixed with corn oil and dextrose. Distal duodenal aspirates were collected every 15 minutes for the next 2-4 hours, until the test meal passed the point of collection. At the end of the first 2-4 hours of sampling, the subject rested for 30 minutes and baseline aspiration of gastric acid and duodenal fluid was obtained before the second meal was administered. Afterward, the subject was given 5 capsules of the test drug (PANCRECARB® MS-16) (16,000 USP units of lipase per capsule) with a standardized liquid Lundh test meal and the sampling procedure described above was repeated for the next 2-4 hours.

<u>Study drug and dose:</u>
A dose of 5 capsules of PANCRECARB® MS-16, Lot # PC-6K09B was ingested with the Lundh test meal in the active treatment phase. This lot, formulated at 100% fill weight and containing 16,000 USP units of lipase, 45,000USP units of amylase and 45,000USP units of protease per capsule (label claim), was also used in clinical study #06-001.

A dose of 5 capsules of Placebo, Lot # PL-012607, was ingested with the Lundh test meal in the Placebo phase. This lot of Placebo was also used in clinical study #06-001(A Randomized, Double-Blind, Placebo-Controlled, Multi-Center, Crossover Study to Evaluate the Effectiveness and Safety of PANCRECARB® MS-16 (pancrelipase) in Reducing Steatorrhea in Children and Adults with Cystic Fibrosis).

Patients must have met all of the following criteria:

1. Documented chronic pancreatitis, alcohol induced chronic pancreatitis or cystic fibrosis;
2. Documented pancreatic enzyme insufficiency as determined by spot fecal elastase-1 <75 mcg/g stool at the time of inclusion in the study;
3. Required daily exogenous enzyme supplementation with commercially available pancreatic enzymes;
4. > 18 years of age;
5. Male and female;
6. Able to swallow capsules;
7. Clinically stable with no evidence of an acute medical condition; and
8. Positive fecal fat (changed to "history of steatorrhea" on 1/09/2007).

Seven subjects completed the study. Demographics of patients who completed the study are summarized in Table 6.

Table 6. Demographics of patients who completed the study

Subject Number	Gender	Diagnosis	Age	Fecal Elastase µg/g	Pancreatic Insufficiency
1001	Male	Chronic pancreatitis	79	<75	Yes
1002	Male	Cystic fibrosis	38	<75	Yes
1003	Male	Chronic pancreatitis	69	<75	Yes
1004	Female	Chronic pancreatitis	36	<75	Yes
1008	Male	Chronic pancreatitis	64	<75	Yes
1010	Male	Chronic pancreatitis	78	<75	Yes
1011	Male	Chronic pancreatitis	79	<75	Yes
		Average	67.5		
		Standard Deviation	16.6		

Subjects were required to stop taking any protein pump inhibitors (PPI) (3 days prior) and gastric acid secretion inhibitors (H2 blockers) (1 day prior).

Reviewer's comments: The sponsor did not claim bioavailability in its proposed labeling. Though the general scheme of the study design is considered acceptable to support the label claims, the sponsor needs to clarify whether inflated balloons were used to ensure that all meal plus PEG perfusate plus endogenous secretion was completely available for aspiration. The sponsor did not describe the exact criterion used to determine the completion of liquid meals were emptied from the stomach and passed the duodenal aspiration sites. However, the length of aspiration study seemed to be long enough to cover the transit time of liquid meal in that part of the GI tract. The sponsor did not measure non-absorable PEG concentrations in the collected aspirates to calculate individual volume correction factors. So its bioavailability estimation was incorrect. The sponsor did not calculate the total amount of lipase recovered during the placebo phase for a more accurate estimation of oral bioavailability.

2.2.2 What was the intubation procedure?

Subjects were fasted for 12 hours and served with a clear liquid diet. Standard upper endoscopy was performed and a gastric pH was obtained. If the gastric pH was > 4, the subject was terminated, and if the pH was < 4 the subject was prepared for endoscopic placement of three Liguory nasal biliary aspiration catheters. One 8.5 fr. catheter was placed in the distal duodenum for aspiration. A 7.0 fr. catheter (with approximately 2.5mm OD) was placed in the first portion of the duodenum for perfusion of PEG (polyethylene glycol marker), and one 7.0 fr. in the stomach for aspiration. A 7.5 fr catheter has an approximate 2.51 mm OD. A photograph illustrating the position of the aspiration catheters is shown below in Fig 1.

Fig 1. Photograph of the position of aspiration catheters

The proximal duodenum was perfused over the study duration with a non-absorbable marker (2.0 mg/mL polyethylene glycol (PEG) solution) via the infusion catheter at a rate of 4 mL/minute. The two “aspiration” catheters were connected to a low vacuum suction. Baseline samples were obtained from the gastric and distal duodenal ports and placed on ice. Two additional baseline samples were obtained every 15 minutes for thirty minutes. Totally three baseline samples were collected from stomach and duodenum, respectively, from each subject.

Thereafter, the subject swallowed 5 capsules of the placebo with a standardized liquid Lundh test meal. Gastric aspirates were collected once every 60 minutes. No more than 5 mL was collected during a 60 minute period. Distal duodenal aspirates were collected every 15 minutes for the next 2-4 hours, until the test meal passed the point of collection. At the end of the first 2-4 hours of sampling the subject rested for 30 minutes and baseline aspiration of gastric acid and duodenal fluid was obtained before the second meal. Afterward, the subject was given 5 capsules of the test drug (PANCRECARB® MS-16) (16,000 USP units of lipase per capsule) with a standardized liquid Lundh test meal and the sampling procedure described above was repeated for the next 2-4 hours. After completion of the last sample collection, an x-ray picture was taken to verify that the suction tubes had remained in the same location in the duodenum.

Due to excessive mucus clogging the duodenal suction ports, only low duodenal volumes could be collected from subjects 1001, 1003, and 1004. The infusion rate for PEG was increased from 2 mL/minute to 4 mL/minute to prevent clogging of the duodenal tube suction ports. The greater PEG infusion rate substantially increased total duodenal sample collection. Duodenal aspirate collections were done with the 4 mL/minute PEG infusion condition for subjects 1008, 1010 and 1011.

Reviewer’s comments: Based on the submitted description, the incubation procedure appears to be reasonable. The sponsor did not provide detailed information about whether balloons were employed to make sure that all the PEG perfusate plus gastric and pancreatic secretion were aspirated completely for a complete recovery of lipase delivered in the duodenum. Clogging of catheters might have influenced the outcome of duodenal lipase recoveries.

2.2.3 What is the bioavailability of Pancrecarb® in the patients with pancreatic insufficiency?

According to the submitted information, the total % aspirate activity recovered for each of lipase, protease, and amylase was calculated using the following equations.

Gastric:

[100% * [Aspirate enzyme activity (U/ml) * total volume collected in a 15-min interval * volume correction factor]/total dose of each enzyme

Where volume correction factor equaled the volume collected in each 15 min interval divided by 31.25 ml. 31.25 ml = (500 ml Lundh Meal/240min) * 15 min

Duodenal:

100% * [Aspirate enzyme activity (U/ml) * total volume collected in a 15-min interval * volume correction factor]/total dose of each enzyme

Where volume correction factor equals the volume collected in each 15 min interval divided by 61.2 ml for subjects 1001, 1003, 1004 or by 91.2 ml for subjects 1008, 1010, and 1011. 61.2 ml = [(500 ml Lundh Meal+480 ml PEG])/240 min]* 15 min. 91.2 ml= [(500 ml Lundh Meal+960 ml PEG)/240min]* 15 min

The concentration of non-absorable marker, PEG, was 2 mg/ml and perfused at 2 ml/min for subjects 1001, 1003, 1004 and at 4 ml/min for the rest.

The sponsor should have used the non-absorable marker, PEG, to correctly determine the volume correction factor. Use of meal volume plus PEG perfusate volume is not accurate as using PEG because the volume of endogenous gastric and pancreatic juice secretion was ignored. It appeared that the sponsor assumed that endogenous secretion was negligible and not substantial in changing the volume of aspirates.

Seven subjects underwent the intubation procedure; six of them yielded sufficient aspiration fluid volume to provide for the appropriate enzymatic analyses. Representative plots of gastric and duodenal enzyme levels after placebo or Pancrecarb are shown in Fig 2 and Fig 3.

Fig 2. Enzyme levels after placebo (subject 1011)

(b) (4)

The figure above illustrates gastric and duodenal pH and enzyme levels in response to Placebo. There is a slight increase in lipase, amylase, and protease activity between 15 minutes (baseline) and 150 minutes in the duodenal phase. The sponsor stated that "The increase in enzyme activity may have been due to salivary amylase, gastric lipase, and some residual secretions from the pancreatic gland." Only a trace level of enzyme activity was observed in the gastric phase. The gastric pH rapidly declined to a low of pH 1.3, while the duodenal pH declined to a lesser degree to pH 4.2. The rise in the duodenal pH between 75 and 150 minutes might have been from endogenous pancreatic bicarbonate secretion and the release of pancreatic bicarbonate or from the Placebo dosage; i.e. Placebo equals (buffer plus other excipients minus the API).

Fig 3. Enzyme levels after Pancrecarb (subject 1011)

(b) (4)

The above figure shows gastric and duodenal pHs and enzyme levels in response to ingestion of PANCRECARB® with the standardized liquid Lundh test meal. There was a considerable increase in lipase, amylase, and protease levels between 15 minutes and 240 minutes in the duodenum. The sponsor stated that “There was also a significant rise in the duodenal pH signifying bicarbonate release from the enteric-coated microspheres that also coincided with the increased levels of lipase, amylase and protease in the duodenal aspirates. The increase in enzyme levels was due to the exogenously administered PANCRECARB® MS-16 capsules as demonstrated by employing SDS-PAGE techniques and by the separation and identification of the protein bands as compared to reference standards.” There was some premature release and low levels of amylase and protease from the enteric-coated microspheres in the stomach (30–195 minutes).

Again, endogenous pancreatic secretion could have raised the duodenal pH as well since it also contains sodium bicarbonate. So the increase in duodenal pH could not be solely attributed to ingestion of PANCRECARB®. Some microspheres might not have been formulated properly, causing a small extent of premature release.

According to the sponsor, salivary human amylase, gastric lipase and protease (pepsin) might have contributed to the presence of these enzymes between 15-30 minutes in subjects 1001 and 1003 after placebo. Subjects 1004, 1008, 1010 and 1011 might have salivary amylase between 15 to 135 minutes after placebo. Subjects 1001 and 1004 had substantial elevation of lipase and protease levels, suggesting possible premature release of Pancrecarb content to gastric fluid (Table 7).

Table 7. Comparison of Peak Time and Peak (Maximum) Enzyme Levels in Phase I (Placebo) and Phase II (PANCRECARB®) Gastric Fluid

Subject Number		Phase I (Placebo) Peak Enzyme Levels USP U/mL, (Peak time, min)			Phase II (PANCRECARB®) Peak Enzyme Levels USP U/mL, (Peak time, min)			
		Amylase	Lipase	Protease	Amylase	Lipase	Protease	
1001 (b) (6)		339 (30)	51 (30)	11 (30)	202 (240)	151 (75)	327 (90)	
1003		19 (15)	4 (15)	4 (15)	14 (75)	ND	124 (75)	
1004		13 (75)	ND	9 (195)	488 (75)	53 (75)	427 (75)	
1008		61 (15)	ND	ND	97 (135)	ND	ND	
1010		112 (135)	ND	ND	10 (75)	ND	44 (135)	
1011		6 (15)	<1 (15)	4 (135)	41 (15)	<1 (15)	43 (75)	
ND= none detected								

Endogenous pancreatic enzymes from pancreatic reserves and salivary amylase, gastric lipase and protease such as pepsin were shown to be present in the duodenal aspirates of subjects who had received the standardized liquid Lundh test meal and Placebo. Amylase levels peaked at 15 to 105 minutes for Subjects 1004 and 1010 in the duodenum during the Placebo phase as illustrated in Table 8.

Table 8. Comparison of Peak Time and Peak Enzyme Levels in Phase I (Placebo) and Phase II (PANCRECARB®) in Duodenal Fluid

Subject Number		Phase I (Placebo) Peak Enzyme Levels USP U/mL, (Peak time, min)			Phase II (PANCRECARB®) Peak Enzyme Levels USP U/mL, (Peak time, min)			
		Amylase	Lipase	Protease	Amylase	Lipase	Protease	
1001 (b) (6)		39 (75)	272 (135)	36 (165)	1003 (105)	315 (105)	1483 (105)	
1003		17 (15)	5 (225)	4 (60)	46 (120)	24 (120)	181 (120)	
1004		190 (15)	183 (15)	39 (15)	249 (105)	301 (165)	382 (75)	
1008		23 (135)	ND	ND	293 (90)	91 (120)	348 (120)	
1010		167 (105)	ND	4 (240)	585 (60)	123 (45)	458 (60)	
1011		5 (30)	3 (30)	2 (75)	67 (60)	10 (75)	121 (120)	
ND=none detected								

Lipase levels also peaked at 15 and 135 minutes for subjects 1004 and 1001. Negligible enzyme levels were noted for Subjects 1003, 1008 and 1011 in the duodenum during Placebo ingestion. In contrast to the Placebo phase, amylase, lipase and protease were present in Phase II in duodenal aspirates of all subjects after they have ingested the standardized liquid Lundh test meal and PANCRECARB® capsules. Peak levels for

amylase, lipase and protease appeared at 45 to 165 minutes and activity levels ranged from 5-190, 0-272 and 0-39 USP units/mL for the Placebo phase, respectively. Peak levels for amylase, lipase, and protease ranged from 46-1003, 10-315 and 121-1483 USP units/mL for the PANCRECARB® phase, respectively.

The detailed calculations used by the sponsor for the total % activity of each enzyme recovered from the gastric or duodenal aspirates are attached in the individual Study Reviews Section and described above in the beginning part of this section. In short, individual enzyme activities collected in the aspirates were first calculated by multiplying the experimentally determined enzyme activity in unit volume by the total volume of aspirate collected in the 15-min interval up to a specific time point. According to the sponsor, the volume correction factor was the total volume of aspirate collected divided by the theoretical maximal volume in that time interval. The sponsor defined the theoretical maximal volume as the volume of the liquid meal for gastric phase or the volume of the liquid meal plus the volume of PEG solution perfused for duodenal phase in a 15-min interval. The experimentally determined activity of each enzyme over the 15-min interval was divided by the volume correction factor for the corrected enzyme activity within the 15-min period, and the total activity of each enzyme over the 4-hr study period was determined by summing up individual 15-min corrected activities. The sponsor should have used the non-absorable marker, PEG, to correctly determine the volume correction factor.

Exogenously administered PANCRECARB® MS-16 (pancrelipase) had Tmax at 45 to 165 minutes post administration of PANCRECARB® with the liquid Lundh test meal. Thiruvengadam et al. (1988) reported that the amount of a given dose of lipase surviving in the duodenum past 30 minutes is <30%. Low lipase activity was present in two patient duodenal aspirates that may have been due to rapid degradation of lipase by the very active proteases. In the present bioavailability study, lipase was recovered from the duodenum in an average of 33.21% (SD:31.24%) (with baseline correction). In vitro dissolution results showed that this lot of PANCRECARB® released 73% of lipase on dissolution at pH 6.0 within 30 minutes.

Placebo phase:
The sponsor did not calculate the % activities recovered for pancreatic enzymes.

Phase II (PANCRECARB®):
A dose of 5 capsules of PANCRECARB® MS-16 was ingested with the Lundh test meal in the active drug phase. Results of individual enzyme activities recovered in gastric or duodenal aspirates are summarized below in Table 9.

Table 9. Quantitative recovery of enzymes from the stomach and duodenum during phase II (active drug phase)

Table 9a. Lipase

LIPASE

Subject Number	Gastric (% Activity Recovered)	Duodenal (% Activity Recovered)
1001	6	52
1003	0	3
1004	2	86
1008	0	30
1010	0	27
1011	0	5
AVERAGE =	1.3	33.8
STDEV =	2	31

Fold Increase from Gastric to Duodenal = *25*

Table 9b. Amylase

AMYLASE

Subject Number	Gastric (% Activity Recovered)	Duodenal (% Activity Recovered)
1001 (b) (6)	15	45
1003	0	4
1004	7	32
1008	2	56
1010	7	94
1011	1	9
AVERAGE =	5.3	40.0
STDEV =	6	33

Fold Increase from Gastric to Duodenal = *8*

Table 9c. Protease

PROTEASE

Subject Number	Gastric (% Activity Recovered)	Duodenal (% Activity Recovered)
1001 (b) (6)	19	68
1003	2	12
1004	7	57
1008	5	56
1010	12	51
1011	1	23
AVERAGE =	7.7	44.5
STDEV =	7	22
	Fold Increase from Gastric to Duodenal =	*6*

* Five (5) capsules of PANCRECARB® MS-16 were consumed with 500 mL standardized liquid Lundh test meal. The five capsules of PANCRECARB® MS-16 contained 80,000 USP units of lipase, 225,000 USP units of amylase and 225,000 USP units of protease. Detailed patient listings, procedures, and calculations are shown in Section 16.2.4.

Reviewer's comments: The sponsor did not discuss the impact of water secretion or absorption in the stomach or duodenum on the pancreatic enzyme activities or on PEG concentration. Apparently, the sponsor assumed that water secretion or absorption does not occur in the stomach or duodenum, or is negligible or too small to be counted in the calculation of enzyme activities recovered.

If there is negligible water secretion or absorption in the stomach or duodenum, the equations used to calculate the enzyme activities recovered are acceptable. The correct way is use of non-absorable marker, PEG, to correct for the diluting or concentrating effect of gastrointestinal water absorption or secretion. The sponsor should have determined duodenal PEG concentrations in each 15-min samples and the fold change of PEG concentration in each sample relative to the original ones, and then used the so-calculated fold change as the correction factor to estimate individual activities recovered.

The sponsor did not correct the activities recovered for baseline levels (human endogenous enzymes). The reviewer recalculated the data with baseline correction only for duodenal enzyme activities recovered since the duodenum is the delivery/action site. The gastric data were not recalculated for baseline correction since enzymes related in the stomach will be destroyed by acidity and not available for action in the duodenum. Mean% (SD) gastric lipase activity recovered was 1.3% (2%). After baseline correction, mean% (SD) duodenal lipase activity recovered was 33.21% (31.24%). Fold increase in lipase activity from gastric to duodenal equals 25.55 (33.21 divided by 1.3). For both amylase and protease activities in the duodenal aspirates, the reviewer did the baseline correction and the results are almost identical to the data without baseline correction. So, the data for amylase and protease activities recovered reported below are without baseline correction. Mean %(SD) gastric amylase activity recovered was 5.3% (6%) and mean %(SD) duodenal amylase activity recovered was 40% (33%). Fold increase in amylase activity from gastric to duodenal is 8. Mean %(SD) gastric protease activity recovered was 7.7% (7%) and mean %(SD) duodenal amylase activity recovered was

44.5% (22%). Fold increase in protease activity from gastric to duodenal is 6. Calculations were based on five capsules of Pancrecarb MS-16 contained 80,000 USP units of lipase, 225,000 USP units of amylase, and 225,000 USP units of protease.

The reviewer recalculated the % activities recovered in duodenal aspirates by taking into account baseline levels. The assumptions are that the baseline levels reflected human endogenous enzymes and the contribution of human endogenous enzymes remained constant before or after drug administration, and that individual enzymes from either source shared individual identical activities. With correction for baseline levels of individual enzymes, the increased enzyme levels in the duodenal aspirates were close to the levels without baseline corrections, and accounted for approximately 33% lipase, 40% amylase and 45% protease recovery from the ingested PANCRECARB® dose of five (5) capsules. The recovered enzyme levels represent 25, 8 and 6-fold increase of lipase, amylase, and protease in the duodenum, respectively, as compared to the levels in the stomach from the exogenously administered PANCRECARB®. Less than 10% of lipase, amylase and protease were released into the stomach from the PANCRECARB® enteric-coated microspheres.

According to some literature, the volume from saliva, gastric secretion, biliary and pancreatic secretion accounts for approximately 6 liter daily. It is estimated approximately 1 liter of water would have been secreted from these sources into aspirates within the 4-hr period. If that was the case, the % activity recovered would have been close to 1.6 fold higher if water secretion had been taken into account in diluting duodenal pancreatic enzyme activities per unit volume.

The sponsor did not calculate the total lipase activity recovered following placebo, resulting form endogenous enzyme secretion. The reviewer calculated the phase I data for individual subjects and the results are described below.

Subject 1001 showed higher duodenal lipase activity following placebo (phase I) than after PANCRECARB®. So was subject 1003. Subject 1004 had endogenous pancreatic lipase secretion equivalent to 52.4% of 80,000 U porcine lipase activity. There are no phase I data reported for subjects 1010 and 1008. There was no lipase secretion following placebo in subject 1011. Based on these results, it is concluded that only a small amount of lipase activity (<10%) was truly attributed to PANCRECARB® administration.

Though the results following PANCRECARB® demonstrated the product was bioavailable with a high degree of variation, it is difficult to determine the actual bioavailability of the product after taking into account the results following placebo. According to the ongoing internal discussions of DPG, the bioavailability study using the intubation procedure is considered unreliable for assessing the delivery of pancreatic enzymes to duodenum. According to a verbal communication with the clinical reviewer of this NDA, Dr. Marjorie Dannis, the pivotal study demonstrated that PANCRECARB® is efficacious. Therefore, the sponsor may not be required repeat the bioavailability study.

2.2.4 What are the enzyme identities recovered in gastric or duodenal aspirates?

The identities of individual enzymes recovered in duodenal aspirates were demonstrated using SDS-PAGE analysis (Fig 4 and Fig 5). SDS-PAGE analysis of gastric and duodenal aspirates showed the appearance of protein bands around 50 kD in molecular weight that corresponds to porcine lipase and porcine pancreatic amylase and protein bands in the 20 – 35 kD in molecular weight that corresponds to porcine pancreatic proteases (b) (4) The appearance of these protein bands at the time points from 45 to 165 minutes coincides with the peaks in measured enzyme activities for lipase, amylase and protease, thus demonstrating that these bioactive proteins with lipase, amylase and protease activities originate from the exogenously administered PANCRECARB® capsules.

Fig 4. SDS-PAGE Fingerprint Analysis – 15% acrylamide Subject 1004 (b) (6); Duodenal Aspirate Analysis

(b) (4)

Fig 5..SDS-PAGE Fingerprint Analysis – 15% acrylamide Subject 1004 (b) (6); Duodenal Aspirate Analysis

(b) (4)

Detailed discussion of the SDS-PAGE separated protein bands for subjects 1001 (b) (6) 1003 (b) (6), 1004 (b) (6), 1008 (b) (6), 1010 (b) (6)), and 1011 (b) (6)) are included in the submission as well.

The SDS-PAGE data are qualitative and supported that the porcine lipase, protease and amylase were present in the duodenal aspirate using proteins of different molecular weights as markers. The 50 KD lipase bands were more intense than other enzyme bands, and were observed in phase II samples but not in phase I samples. One band of higher molecular weight than porcine 50 KD lipase band was observed in duodenal phase I aspirates but not in Pancarcarb or duodenal phase II aspirates.

Reviewer's comments: The molecular weight of purified human pancreatic lipase is approximately 46,000 D. Based on the fact that lipase activities were observed in phase I samples following placebo, human lipase should have been present in those samples. The sponsor did not provide the band markers corresponding to the molecular weights of human lipase. It is not clear whether the method used by the sponsor provided a high enough resolution to separate human lipase from porcine lipase. Combining the results from Phase I and Phase II aspirates, the results did indicate that the bands corresponding to the size and molecular weight of porcine lipase were present in duodenal aspirates. A more accurate method is use of a Western blotting technique with the monoclonal antibodies to porcine lipase to further firmly identify the presence of porcine lipase in duodenal aspirates.

2.2.5 Is the product stable when mixed with applesauce?

Rationale for conducting this study: Pancrecarb® (pancrelipase) delayed release capsules are to be taken with liquid at the start of the meal. If patients have difficulty

swallowing the capsule, there needs to be an alternative medium for the patients to swallow Pancrecarb®. Applesauce could be used to deliver the capsule content as the medium for mixing with microspheres. The sponsor conducted an in vitro study to determine the lipase stability after Pancrecarb® MS-4 microspheres were mixed with, and exposed to, applesauce for 0, 20, 30 minutes, and MS-8 and MS-16 microspheres were mixed with, and exposed to applesauce for 0, 30, and 40 minutes at room temperature. Gerber applesauce, stage 2(2nd food) (pH 3.5) was used. The mixture was then washed with at least 200 ml cold water and the washing was repeated twice. The time spent in washing/decanting/recovery of the microspheres free of applesauce was less than 5 minutes. The sponsor referenced USP 30/NF25 (volume 30) for its assay of the lipase activity in pancrelipase.

Regents and solution:
Reagents and solution for lipase assay were prepared according to DCI TM-6013 (<USP30>). The assay were performed using Mettler Toledo T70 titrator or TIM 856, Titration Manager. The products used in the study are summarized in Table 10.

Table 10. Products used in the study

PANCRECARB® Lot to be tested for total activity and applesauce	Number of capsules opened	Weight of the microspheres exposed to 10 mL applesauce and for total lipase activity of the capsule
PANCRECARB® MS-4 (three lots)	N=2	425-500 mg
PANCRECARB® MS-8 (three lots)	N=2	829-925 mg
PANCRECARB® MS-16 (three lots)	N=2	1000-1100 mg

USP reference standard for pancrelipase or an in-house reference standard was used as a reference control to establish day-to-day assay variability. Results of MS-4, MS-8, and MS-16 after exposing to applesauce at room temperature are summarized in Tables 11, 12 and 13, respectively

Table 11. Results of MS-4 after exposing to applesauce at room temperature

	% Lipase potency retained			
Material Tested	After 0 minute exposure of the capsules to air at room temperature (23±2°C)	After 50 minutes exposure of the capsules to air at room temperature (23±2°C)	After 40 minutes exposure of the microspheres to applesauce at room temperature	After 50 minutes exposure of the microspheres to applesauce at room temperature
PANCRECARB® MS-4, Lot# PC-7C04A	100 (n=2)	102 102	92	91
			89	85
			98	--
PANCRECARB® MS-4, Lot# PC-7D06A	100 (n=2)	102 101	87	85
			89	78
			90	84
PANCRECARB® MS-4, Lot# PC-7A02A	100 (n=2)	99 99	86	86
			91	87
			90	87
	Mean ± S.D.	**101 ± 1.5 (pass)**	**90 ± 3.5 (pass)**	**85 ± 3.7 (fail)**
	% RSD	**1.5**	**3.9**	**4.4**

% Lipase potency retained=
(Lipase activity of PANCRECARB® MS-4 after exposure to applesauce or room temperature/ Lipase activity of PANCRECARB® MS-4 at 0 minute) x100

Reviewer's comment: The MS-4 microspheres were stable after capsule exposure to air at room temperature for 50 minutes with no change in % of lipase activity in the microsphere, and lost less than 10% of lipase activity after exposure to applesauce for 40 minutes with 90% of lipase activity remained. The lipase activity of MS-4 microspheres dropped to 85% after 50 minutes of exposure to applesauce. The 90% activity remained after 40 min exposure to applesauce is deemed acceptable.

Table 12. MS-8 after exposing to applesauce at room temperature

	% Lipase potency retained			
Material Tested	After 0 minute exposure of the capsules to air at room temperature (23±2°C)	After 70 minutes exposure of the capsules to air at room temperature (23±2°C)	After 60 minutes exposure of the microspheres to applesauce at room temperature	After 70 minutes exposure of the microspheres to applesauce at room temperature
PANCRECARB® MS-8, Lot# PC-7B03A	100 (n=2)	101 103	87	90
			91	88
			85	91
PANCRECARB® MS-8, Lot# PC-7D05A	100 (n=2)	103 103	94	87
			94	92
			95	94
PANCRECARB® MS-8, Lot# PC-6I06A	100 (n=2)	106 103	94	89
			87	84
			88	84
	Mean ± S.D.	**103 ± 1.6 (pass)**	**91 ± 3.8 (pass)**	**89 ± 3.4 (fail)**
	% RSD	**1.6**	**4.2**	**3.8**

% Lipase potency retained=
(Lipase activity of PANCRECARB® MS-8 after exposure to applesauce or room temperature/ Lipase activity of PANCRECARB® MS-8 at 0 minute) x100

Reviewer's comment: The MS-8 microspheres were stable after capsule exposure to air at room temperature for 70 minutes with no change in % of lipase activity in the microsphere, and lost less than 10% of lipase activity after exposure to applesauce for 60 minutes with 90% of lipase activity remained. However, the lipase activity of MS-8 microspheres dropped to 91 % and 89 % after 60 and 70 minutes of exposure to applesauce, respectively. The 91% activity remained after 60 minute exposure to applesauce is acceptable.

Table 13. MS-16 after exposing to applesauce at room temperature

	% Lipase potency retained			
Material Tested	After 0 minute exposure of the capsules to air at room temperature (23±2°C)	After 60 minutes exposure of the capsules to air at room temperature (23±2°C)	After 50 minutes exposure of the microspheres to applesauce at room temperature	After 60 minutes exposure of the microspheres to applesauce at room temperature
PANCRECARB® MS-16, Lot# PC-7A01B	100 (n=2)	100 98	96	85
			95	91
			97	94
PANCRECARB® MS-16, Lot# PC-7E07B	100 (n=2)	102 102	89	85
			94	83
			88	82
PANCRECARB® MS-16, Lot# PC-7H09B	100 (n=2)	94 99	90	90
			94	85
			96	91
	Mean ± S.D.	**99 ± 3.0 (pass)**	**93 ± 3.6 (pass)**	**87 ± 4.2 (fail)**
	% RSD	**3.0**	**3.9**	**4.8**

% Lipase potency retained=
(Lipase activity of PANCRECARB® MS-16after exposure to applesauce or room temperature/ Lipase activity of PANCRECARB® MS-16 at 0 minute) x100

Reviewer's comment: The MS-16 microspheres were stable after capsule exposure to air at room temperature for 60 minutes with no change in % of lipase activity in the microsphere, and lost less than 10% of lipase activity after exposure to applesauce for 50 minutes with 90% of lipase activity remained. However, the lipase activity of MS-16 microspheres dropped to 93% and 87% after 50 and 60 minutes of exposure to applesauce, respectively. The 93% activity left after 50 min exposure is acceptable.

In summary, Pancrecarb® microspheres, MS-4, MS-8 and MS-16, were stable after exposure to applesauce at room temperature for 40 min, 60 min, and 50 min, respectively. The study results support the use of applesauce as a medium to facilitate ingestion of PANCRECARB® microspheres.

2.3 General Biopharmaceutics

2.3.1 Is the proposed formulation identical to the one used for the pivotal clinical studies?

(b) (4) dosage strengths have been developed: (b) (4) MS-8 (8,000 Lipase units) or MS-16 (16,000 Lipase units). The products are formulated with (b) (4) carbonate/bicarbonate). (b) (4) The comparative formulations of PANCRECARB® are summarized in Table 15.

Table 15. Comparative Formulations of PANCRECARB®

Ingredient	(b) (4) MS-8 (Kg)	MS-16 (Kg)	(b) (4) MS-8 (%w/w)	MS-16 (%w/w)
Pancrelipase USP, (b) (4) 1206	(b) (4)		(b) (4)	
Pancrelipase USP, (b) (4) 1208				
Sodium Carbonate (b) (4) NF				
Sodium Bicarbonate, USP				
Sodium Starch Glycolate. NF				
Ursodiol, USP				
Polyvinylpyrrolidone (PVP), USP				
Cellulose Acetate Phthalate, NF				
Diethyl Phthalate				
Talc, USP				
(b) (4)				
Total			100.0	100.0

(b) (4)

2.4 Analytical Section

2.4.1 What analytical methods were used to assess concentrations?

Activities of amylase, protease, and lipase in the clinical samples (both gastric and duodenal intestinal samples) collected in the bioavailability study (#092206) were assayed with commercial kits.

Amylase: Amylase activity was assayed using Alpha-amylase test (FDA's 510 (k) number K870746). Amylase solutions (USP Pancretin Amylase and Protease RS) were prepared at 20 mg/ml in buffer. Amylase reagent was re-adjusted to pH 6.8.

Protease: The suitability of the assay in duodenal fluid was determined using USP Reference Standards for Protease (USP Pancreatin Amylase and Protease RS) with a fluorescent-labeled protein, fluorescein isothiocyanate casein (FITC-casein), as substrate. Following acid precipitation to remove undigested protein or large peptides, the fluorescence intensity of the small peptides in the supernatant was measured at an excitation wavelength of 485 nm and an emission wave length of 530 nm. Protease solutions (USP Pancretin Amylase and Protease RS) were prepared at 20 mg/ml in buffer.

Lipase: Lipase activity was assayed using Lipase-Esterase Color Photometric lipase as Lipase Color Test (FDA's 510 (k) number K897150). Lipase solutions (USP Pancretin Lipase RS) were prepared at 40 mg/ml in water. Lipase reagent activator was re-adjusted to pH 9.0.

Reviewer's comments: According to the CDRH web site, the product associated with 510(K) number K897150, is a lipase color (toyo) serum lipase test kit which was

approved Feb 26, 1990
(http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?ID=78630). Therefore the testing method is considered acceptable.

2.6.2 Are the analytical assay methods adequately validated?

Amylase: In terms of inter-assay precision, the mean relative %RSD (CV%) ranged from 6.1% to 7.6% for the concentration range of 0.44 to 6.96 USP U/ml. Mean intra-analyst precision between 0.44 and 6.96 USP U/ml ranged from 1.8% to 10.2%. The assay method was linear (r^2 of 0.998) within the concentration range of 0.44-6.96 U/ml. The % recovery ranged from 89.9% to 101.4% at 0.44 U/ml and 106.3% at 6.96 U/ml.

Protease: In terms of inter-assay precision, the mean relative %RSD (CV%) ranged from 11.1% to 21.7% between 0.62 and 9.92 USP U/ml. Over the concentration range of 0.62 and 9.92 USP U/ml, the mean intra-analyst precision (%RSD) ranged from 7.5 to 32.7%. The assay method was linear (r^2 of 1) within the concentration range of 0.62-9.92 U/ml. The % recovery was 103% at 4.96 U/ml and 109% at 7.44 U/ml.

Lipase: In terms of inter-assay precision, the mean relative %RSD (CV%) ranged from 9.5% to 11.9% between 0.265 and 4.24 USP U/ml. Over the concentration range of 0.265 and 4.24 USP U/ml, the mean intra-analyst precision (%RSD) ranged from 10.1 to 12.3%. The assay method was linear (r^2 of 0.999) within the concentration range of 0.265-4.24 U/ml. The mean% (CV%) recovery was 56.5% (24.1%) at 0.133 U/ml and 96.7% (14.1%) at 4.24 U/ml.

Reviewer's comments: For amylase and protease activity, the assay methods are considered appropriately validated. For lipase, Though the mean% (CV%) recovery was low at 0.133 U/ml, the lipase concentrations in duodenal aspirate samples were all much higher than 0.133 U/ml. In subjects 1101 and 1003, there were some samples with lipase concentrations lower than 4.24 U/ml, and in other subjects, the majority of duodenal aspirate samples showed lipase concentrations greater than 4.24 U/ml. Based on this observation, the mean% (CV%) recovery reported is considered acceptable.

3 Detailed Labeling Recommendations

Section 2 of the annotated labeling:

2. DOSAGE AND ADMINISTRATION

(b) (4)

The above paragraph is recommended to be revised as shown below.

(b) (4)

(b) (4)

Section 12 of the annotated labeling:

12. CLINICAL PHARMACOLOGY

(b) (4)

The above paragraph is recommended to be revised as follows.

(b) (4)

4 Summary of Individual Studies and Clinical Development

Protocol #092206 October 15, 2008

SPONSOR:	Digestive Care, Incorporated 1120 Win Drive Bethlehem, PA 18017 Telephone. (610) 882-5950
PRODUCT:	PANCRECARB® MS-16, Digestive Care Inc.
PROTOCOL TITLE:	Bioavailability of Pancreatic Enzymes in the Human Upper Intestine (duodenum) from PANCRECARB® (pancrelipase), Delayed Release Capsules, Buffered and Enteric-Coated Microspheres
PRINCIPAL INVESTIGATOR:	Frank R. Burton, MD Ashish Chopra, MD St. Louis University Gastroenterology and Hepatology Endoscopy Unit 3545 Lafayette, 2nd Floor St. Louis, MO 63104
STUDY PERIOD:	15 April 2007 to 1 August 2008
STUDY OBJECTIVES:	To demonstrate the intestinal bioavailability of lipase, amylase, and protease from PANCRECARB® when administered orally with a standardized liquid Lundh test meal to exocrine pancreatic insufficient patients.
STUDY DESIGN AND DURATION OF TREATMENT:	Single site, open label, bioavailability
NUMBER OF SUBJECTS:	11
TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION:	A dose of 5 capsules of PANCRECARB® MS-16 (16,000 USP units of lipase per capsule) given orally with a standardized liquid Lundh test meal.
CONTROL PRODUCT, DOSE AND MODE OF ADMINISTRATION	A dose of 5 capsules of Placebo given orally with a standardized liquid Lundh test meal.
SAFETY MEASUREMENT:	Adverse events

DATA ANALYSIS:	The results will be presented using descriptive statistics; mean, standard deviations, maximum and minimum for enzyme activities. Cumulative postprandial enzyme output recovered in the aspirates will be compared by calculating areas over the collection period between the gastric and distal duodenal aspirates. Comparisons between the cumulative enzyme activities, between the gastric and distal duodenal aspirates, will be performed by paired t-test.
SUMMARY OF BIOAVAILABILITY RESULTS:	The bioavailability of lipase, amylase, and protease enzymes from exogenously administered PANCRECARB® MS-16 (pancrelipase) demonstrated peak enzyme levels in the duodenum at 45 to 165 minutes post administration of PANCRECARB® with the Lundh test meal. The increased enzyme levels in the duodenal aspirates correspond to a recovery of activity of 34% ± 31 lipase, 40% ± 33 amylase and 45% ± 22 protease of the ingested PANCRECARB® dose (five (5) capsules). Minimal amounts of lipase, amylase and protease were released into the stomach from the PANCRECARB® enteric-coated microspheres. SDS-PAGE analysis of gastric and duodenal aspirates showed the appearance of protein bands around 50 kD in molecular weight that corresponds to porcine pancreatic lipase, and porcine pancreatic amylase, as well as protein bands in the 20 – 35 kD range in molecular weight that correspond to porcine pancreatic proteases (b) (4) (b) (4) The appearance of these protein bands at the time points from 45 to 165 minutes coincide with the peaks in measured enzyme levels for lipase, amylase and protease, thus conclusively demonstrating that these bioactive proteins with lipase, amylase and protease activities originate from the exogenously administered PANCRECARB® capsules and are released at the site of action (gastrointestinal tract).
SUMMARY OF SAFETY RESULTS:	One patient experienced a mild gagging event. Another experienced mild intermittent nausea. Neither event was considered by the investigator to be related to the study drug.
CONCLUSIONS:	Based on the results of this study, it is concluded that the bioavailability of the exogenously administered PANCRECARB® (pancrelipase) capsules in chronic exocrine pancreatic insufficient patients has been successfully demonstrated in the duodenum and, as such, satisfies the NDA requirements for the demonstration of bioavailability for pancreatic enzyme products (PEP) at the site of action (the gastrointestinal tract).

A. Procedure for Adjustment of Duodenal Aspirate Activities by Volume Correction

1. Determine the total enzyme activity for a collection time point: multiply experimentally-determined enzyme activity value (U/mL) by the total collection volume for that time point (mL). This gives a total enzyme activity for that collection time point (U).
2. Determine the maximum volume of aspirate that could theoretically be obtained during Phase II.
    a. PEG Infusion Contribution
        i. Patients 1001, 1003, 1004: PEG infusion rate was 2.0 mL/min. Since Phase II was 240 minutes in length, the total amount of aspirate available from the PEG infusion would be 2.0 mL/min * 240 min = 480 mL
        ii. Patients 1008, 1010, 1011: PEG infusion rate was 4.0 mL/min. Since Phase II was 240 minutes in length, the total amount of aspirate available from the PEG infusion would be 4.0 mL/min * 240 min = 960 mL
    b. Lundh Meal Contribution = 500 mL administered with PANCRECARB® MS-16 capsules.
    c. Maximum volume of aspirate for Subjects 1001, 1003, 1004 = 480 mL from PEG Infusion + 500 mL from Lundh Meal = 980 mL
    d. Maximum volume of aspirate for Subjects 1008, 1010, 1011 = 960 mL from PEG Infusion + 500 mL from Lundh Meal = 1460 mL
3. Determine the maximum volume of aspirate that could theoretically be obtained for each collection time point.
    a. Patients 1001, 1003, 1004: 980 total mL ÷ 240 min = 4.08 mL/min. Samples were collected every 15 minutes: 4.08 mL/min * 15 min = 61.2 mL
    b. Patients 1008, 1010, 1011: 1460 total mL ÷ 240 min = 6.08 mL/min. Samples were collected every 15 minutes: 6.08 mL/min * 15 min = 91.2 mL
4. Calculate the Volume Correction Factor
    a. Patients 1001, 1003, 1004: Divide the total duodenal collection volume for a given time point by 61.2 mL.
    b. Patients 1008, 1010, 1011: Divide the total duodenal collection volume for a given time point by 91.2 mL.
5. Divide the total enzyme activity (as determined in Step #1) by the Volume Correction Factor to give the Corrected Total Enzyme Activity for that time point.
6. Repeat Steps #1-6 for all three enzymes (lipase, amylase and protease) and for each collection point of Phase II. For each enzyme, add all Corrected Total Enzyme Activities for all time points of Phase II to give the Recovered Total Enzyme Activity of that enzyme for the PANCRECARB® phase of the study.

A. Procedure for Adjustment of Duodenal Aspirate Activities by Volume Correction (cont'd)

7. Calculate the Total % Activity Recovered
    a. Lipase ⇒Divide the Recovered Total Enzyme Activity by 80,000 U (total units lipase available from 5 capsules of PANCRECARB® MS-16).
    b. Amylase ⇒Divide the Recovered Total Enzyme Activity by 225,000 U (total units amylase available from 5 capsules of PANCRECARB® MS-16).
    c. Protease ⇒Divide the Recovered Total Enzyme Activity by 225,000 U (total units protease available from 5 capsules of PANCRECARB® MS-16).

B. Procedure for Adjustment of Gastric Aspirate Activities by Volume Correction

1. Determine the total enzyme activity for a collection time point: multiply experimentally-determined enzyme activity value (U/mL) by the total collection volume for that time point (mL). This gives a total enzyme activity for that collection time point (U).
2. Determine the maximum volume of aspirate that could theoretically be obtained during Phase II.
   a. Lundh Meal Contribution = 500 mL administered with PANCRECARB® MS-16 capsules.
   b. Maximum volume of aspirate for Subjects 1001, 1003, 1004, 1008, 1010, 1011 = 500 mL from Lundh Meal
3. Determine the maximum volume of aspirate that could theoretically be obtained for each collection time point.
   a. Patients 1001, 1003, 1004, 1008, 1010, 1011: 500 total mL ÷ 240 min = 2.08 mL/min. Samples were collected every 15 minutes: 2.08 mL/min * 15 min = 31.25 mL
4. Calculate the Volume Correction Factor
   a. Patients 1001, 1003, 1004, 1008, 1010, 1011: Divide the total duodenal collection volume for a given time point by 31.25 mL.
5. Divide the total enzyme activity (as determined in Step #1) by the Volume Correction Factor to give the Corrected Total Enzyme Activity for that time point.
6. Repeat Steps #1-6 for all three enzymes (lipase, amylase and protease) and for each collection point of Phase II. For each enzyme, add all Corrected Total Enzyme Activities for all time points of Phase II to give the Recovered Total Enzyme Activity of that enzyme for the PANCRECARB® phase of the study.
7. Calculate the Total % Activity Recovered
   a. Lipase ⇒Divide the Recovered Total Enzyme Activity by 80,000 U (total units lipase available from 5 capsules of PANCRECARB® MS-16).
   b. Amylase ⇒Divide the Recovered Total Enzyme Activity by 225,000 U (total units amylase available from 5 capsules of PANCRECARB® MS-16).
   c. Protease ⇒Divide the Recovered Total Enzyme Activity by 225,000 U (total units protease available from 5 capsules of PANCRECARB® MS-16).

B. Procedure for Adjustment of Duodenal Aspirate Activities by Volume Correction (Cont'd)

8. Calculate the Total % Activity Recovered
   a. Lipase ⇒Divide the Recovered Total Enzyme Activity by 80,000 U (total units lipase available from 5 capsules of PANCRECARB® MS-16).
   b. Amylase ⇒Divide the Recovered Total Enzyme Activity by 225,000 U (total units amylase available from 5 capsules of PANCRECARB® MS-16).
   c. Protease ⇒Divide the Recovered Total Enzyme Activity by 225,000 U (total units protease available from 5 capsules of PANCRECARB® MS-16).

Fingerprint Analysis of Gastric and Dudenal Aspirate by SDS-PAGE

BACKGROUND

Polyacrylamide gel electrophoresis is one of the most frequently used techniques for the analysis of proteins in a sample due to its sensitivity and ability to clearly and quickly resolve the numerous protein constituents of a sample into "bands." Gel electrophoresis typically involves the migration of proteins through a gel matrix upon application of an electrical current. A sundry of types of gel electrophoresis can be used depending on the type of analysis required. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) incorporates sodium dodecyl sulfate, an anionic detergent, in sufficient excess to denature and fully saturate all proteins in a sample, giving them a net negative charge and a uniform charge-to-mass ratio. β-mercaptoethanol is used as a reducing agent to reduce disulfide bonds and eliminate protein secondary structure. Since proteins migrate through an SDS gel based primarily on their size, molecular weights for sample proteins can be determined using molecular weight standards. After any type of electrophoretic separation, bands of protein can be visualized with stains.

Bio-Rad Precast Gel Systems provide a wide variety of polyacrylamide gels for native, SDS and IEF experiments. Each batch is analyzed to ensure quality and uniformity, which eliminates many of the pitfalls of hand-casting gels. The Criterion™ precast gel system utilizes mid-size polyacrylamide gels and provides high-resolution results with excellent reproducibility. Criterion™ Tris-HCl gels are made without SDS in an array of acrylamide percentages so they can be used for both SDS and native electrophoresis.

ELECTROPHORETIC SEPARATION: PROCEDURE

** NOTE: Gastric and duodenal samples are of human origin and must be treated with care. Appropriate universal precautions such as gloves, safety glasses and lab coats must be worn at all times. All laboratory supplies (i.e. pipet tips, microcentrifuge tubes, etc.) that come in contact with these samples must be placed in red biohazard bags and disposed of properly. All laboratory surfaces (i.e. bench tops, sinks, etc.) must be cleaned with a bleach solution such as Clorox Clean-Up and 70% isopropyl alcohol at least once daily to insure that the work environment remains sanitary.*

(b) (4)

(b) (4)

Study: Lipase stability of enteric coated pancrecarb microspheres when exposed to applesauce

STUDY OBJECTIVE

The objective of this study is to determine lipase stability when PANCRECARB® MS-4 microspheres are exposed to applesauce for 0, 20, and 30 minutes and MS-8 and MS-16 microspheres are exposed to applesauce for 0, 30, and 40 minutes at room temperature.

HYPOTHESES

We hypothesize that since the protective enteric coating of the microspheres is resistant to low pH, exposing it to low pH food such as applesauce will not decrease the lipase potency significantly provided the contact time i.e., the time taken to consume applesauce mixed with microspheres is practical, that is, it simulates a real life situation.

Study Design:

Study design will be based on the pilot study results* that 10 minute exposure of the e.c. microspheres to low pH food, such as applesauce, did not decrease lipase potency significantly (>90% lipase potency retained).

B. Selection criteria:

The proposed experiment will be carried out using applesauce i.e. baby food available from food stores. The brand of applesauce chosen for the study is based on pilot study* results. The applesauce brand that showed maximum detriment to the enteric-coated microspheres and loss in lipase potency is Gerber, Stage 2 applesauce.

Test Material

PANCRECARB® MS-4, MS-8 and MS-16 enteric coated microspheres and Gerber Applesauce, stage 2 (2nd food) will be used for this study. United States Pharmacopoeia (USP) reference standard for pancrelipase (lot# I1E327) or an in-house reference standard will be used as a reference control to establish day-to-day assay variability.

Reagents and Solutions:

Reagents and solutions for lipase assay will be prepared according to DCI TM-6013 (<USP 30>). The assay will be performed using Mettler Toledo T70 titrator or TIM 856, Titration Manager.

Experimental Methods:

1 Total lipase activity of the capsule:
Total lipase activity of the capsule will be determined by exposing the capsules to room temperature conditions for 0, 20, and 30 minutes for PANCRECARB® MS-4 microspheres and 0, 30, and 40 minutes for PANCRECARB® MS-8 and MS-16 microspheres. After the exposure to room temperature, the capsules will be opened and weighed accurately and transferred to a 50 mL mortar. The microspheres will be ground up using cold distilled water and made up to volume and assayed for lipase activity as directed in TM-6013, Rev. 3. Refer to Table 1 for the details of weights and volume of stock solution preparation for the assay.

Stability in Applesauce:

The stability experiment will be carried out at room temperature using Petri dishes. Fixed amount (10 ml) of applesauce will be placed in Petri dishes, and content of two (2) PANCRECARB® capsules will be mixed with it. The mixture will be allowed to stand for 0, 20, and 30 minutes for MS-4 and 0, 30, and 40 minutes for MS-8 and MS-16 after which the microspheres will be recovered by washing the content into a 500 ml beaker with at least 200 ml of distilled water. The microspheres are expected to settle down at the bottom of the beaker within 1-minute due to the difference in the density of the microspheres. The diluted applesauce will be decanted carefully without losing the microspheres. The process of washing the microspheres with distilled water will be repeated 2 x times to get rid of the residual applesauce. The total time for the washing/decanting/recovery of the microspheres free of applesauce will be < 5 minutes. The recovered microspheres then will be ground up in cold distilled water and assayed for lipase activity following DCI TM-6013, Rev. 3. Refer to Table 1 for the details of weights and volume of stock solution preparation for the assay.

Table 1

PANCRECARB® Lot to be tested for total activity and applesauce	Number of capsules opened	Weight of the microspheres exposed to 10 mL applesauce and for total lipase activity of the capsule	Volume (stock solution)	Stock solution to be pipetted for dilution	Make up to total volume (second dilution)
PANCRECARB® MS-4 (three lots)	N=2	425-500 mg	1000 mL	No dilution	--
PANCRECARB® MS-8 (three lots)	N=2	829-925 mg	500 mL	10 mL	50 mL
PANCRECARB® MS-16 (three lots)	N=2	1000-1100 mg	500 mL	15 mL	100 mL

Statistical Methods and Considerations:

Sample size: contents of two (2) capsules will be exposed to applesauce for the above defined time intervals for MS-4, MS-8, and MS-16 microspheres, respectively. For the details of number of determinations, refer to Table 2. The testing will be conducted for three (3) different lots of PANCRECARB® strengths.

Table 2

Name of PANCRECARB® Lot to be Tested	Exposure time for the capsule to room temperature: 0 min.	Exposure time for the capsule to room temperature: 20 min.	Exposure time for the capsule to room temperature: 30 min.	Exposure time for the microspheres to applesauce at room temperature: 20 min.	Exposure time for the microspheres to applesauce at room temperature: 30 min.
MS-4 Lot #PC-7C04A	N=2 (duplicate assay)	N=2 (duplicate assay)	N=2 (duplicate assay	N=1	N=1
				N=1	N=1
				N=1	N=1
MS-4 Lot #PC-7D06A	N=2 (duplicate assay)	N=2 (duplicate assay)	N=2 (duplicate assay	N=1	N=1
				N=1	N=1
				N=1	N=1
MS-4 Lot #PC-7A02A	N=2 (duplicate assay)	N=2 (duplicate assay)	N=2 (duplicate assay	N=1	N=1
				N=1	N=1
				N=1	N=1
Total number of assays	N=6	N=6	N=6	N=9	N=9

G. Data Collection and Analysis:

After all the assays are completed the following parameters will be reported.

1. Applesauce brand and stages of the applesauce tested.
2. pH of the applesauce tested.
3. Time of exposure of the PANCRECARB® microspheres to applesauce and PANCRECARB® capsules.
4. Percent (%) lipase potencyof the capsule retained after exposure to room temperature.
5. Percent (%) lipase potency retained after exposure to applesauce.

ACCEPTANCE CRITERIA

The % of total activity (potency) retained after the microspheres are exposed for a different amount of time (20 & 30 minutes for MS-4 and 30 & 40 minutes for MS-8 and MS-16 microspheres) to the applesauce is not less than 90% of the labeled claim.

INGREDIENTS	mg/Capsule			% w/w			Function
	(b) (4)	MS-8	MS-16	(b) (4)	MS-8	MS-16	
Pancrelipase, USP (b) (4) 1206 (b) (4) 1208			(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 (b) (4)					100.0	100.0	

** Adjusted based on lipase activity

4.3.1. Cover sheet and OCP Filing/Review Form

Cover Sheet and OCP Filing/Review Form

OFFICE OF CLINICAL PHARMACOLOGY

NEW DRUG APPLICATION FILING AND REVIEW FORM

1. General Information About the Submission

	Information		Information
NDA Number	22-175	Brand Name	Pancrearb
OCPB Division (I, II, III)	DCP III	Generic Name	Pancrelipase
Medical Division	GI	Drug Class	Pancreatic enzyme product
OCPB Reviewer	Tien-Mien Chen, Ph.D.	Indication(s)	Exocrine Pancrelipase Insufficiency
OCPB Team Leader	Sue-Chih Lee, Ph.D.	Dosage Form	DR capsules
		Dosing Regimen	Pancreatic enzyme replacement therapy
Date of Submission	10/29/08	Route of Administration	Oral
Estimated Due Date of OCPB Review	06/20/09	Sponsor	Digestive Care, Inc.
Medical Division Due Date	06/22/09	Priority Classification	S (10 months)
PDUFA Due Date	08/28/09		

(a) Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	1	1	
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
HEALTHY VOLUNTEERS-				
single dose:				
multiple dose:				
PATIENTS-				
single dose:	X	2	2	One *in vivo* intubation study plus one in vitro stability study
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				

geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**3**	**3**	
(a)				

(b) Filability and QBR comments		
	"X" if yes	***(i) Comments***
Application filable ?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable. Clinpharm IR on *in vitro* stability study assay validation has been sent to the sponsor.
QBR questions (key issues to be considered)	**What is the % recovery of pancrelipase from duodenal aspiration after dosing to patients?**	
Other comments or information not included above		
Primary reviewer Signature and Date	**Tien-Mien Chen, Ph.D. 01/27/09**	
Secondary reviewer Signature and Date	**Sue-Chih Lee, Ph.D. 01/27/09**	

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

/s/

Jane Bai
6/9/2009 01:23:59 PM
BIOPHARMACEUTICS

Jang-Ik Lee
6/9/2009 01:32:48 PM
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