

## CLINICAL PHARMACOLOGY REVIEW

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|---------------------------|--------------------------------|
| NDA                       | <b>22-175</b>                  |
| Drug Name                 | <b>PERTZYE™ (pancrelipase)</b> |
| Description of Submission | <b>Resubmission</b>            |
| Submission Date           | <b>11/18/11</b>                |
| Date Received             | <b>11/18/11</b>                |
| Review Type               | <b>Priority (6 months)</b>     |
| Primary Reviewer          | <b>Dionna Green, M.D.</b>      |
| Team Leader               | <b>Yow-Ming Wang, Ph.D.</b>    |
| OCP Division              | <b>DCP 3</b>                   |
| OND Division              | <b>DGIEP</b>                   |
| Sponsor                   | <b>Digestive Care, Inc.</b>    |

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|-----------------------------|--|
| Formulation(s); Strength(s) | <b>Delayed-release capsules;<br/>MS-8 (8,000 USP units of lipase/28,750 USP units<br/>of protease/30,250 USP units of amylase)<br/>MS-16 (16,000 USP units of lipase/57,500 USP<br/>units of protease/60,500 USP units of amylase)</b> |
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| Proposed Indication | <b>Treatment of exocrine pancreatic insufficiency due<br/>to cystic fibrosis or other conditions</b> |
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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

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)

(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**

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 originally proposed 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.)

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 (b) (4)) 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 validation 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:

*“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)

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.

## **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:

$$\text{Lipase activity (U/mg)} = \text{mL NaOH/min} * \text{N NaOH} * 1000 / \text{mg sample assayed}$$

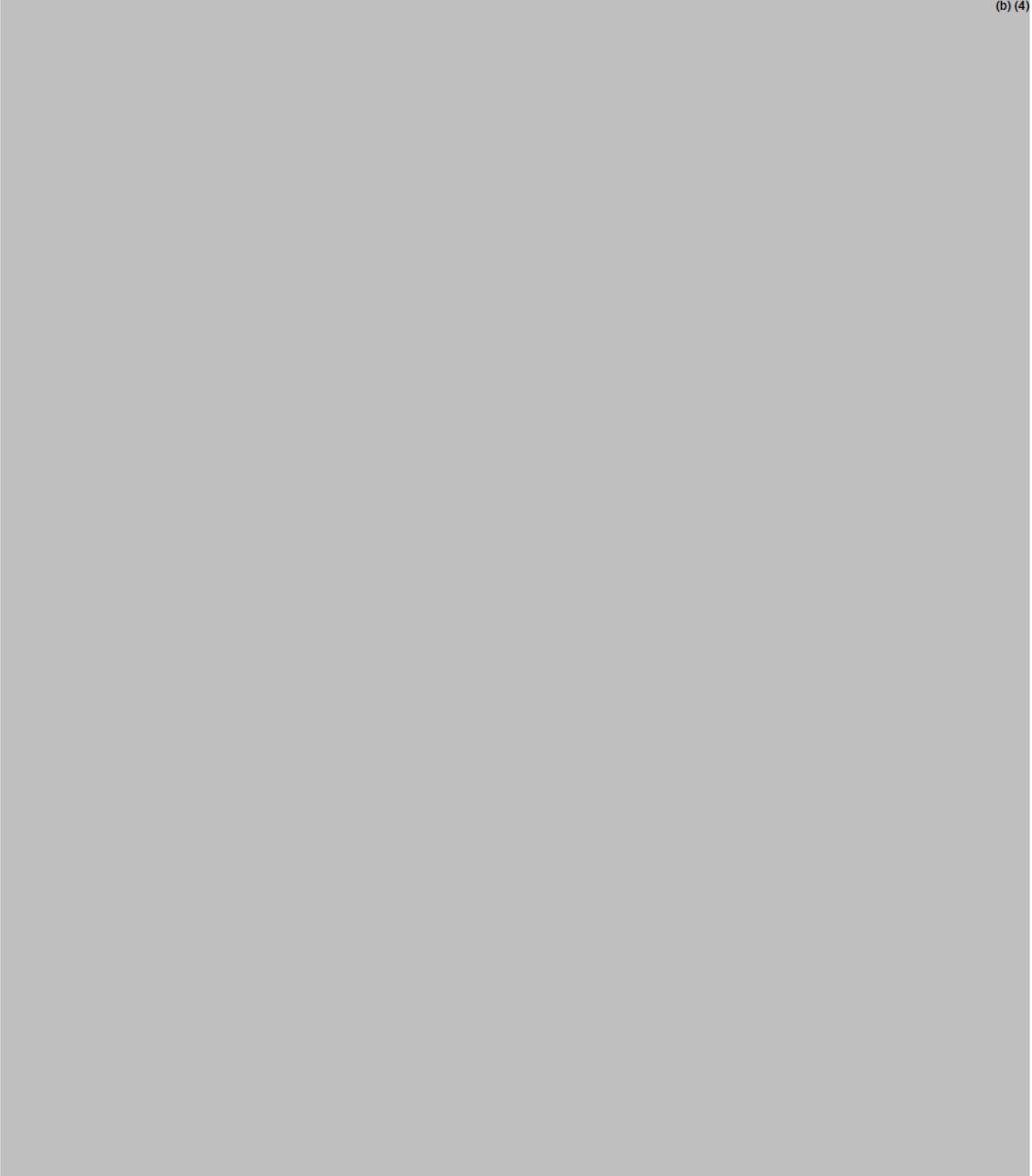
As documented in TMV-050, the assay demonstrates acceptable intra-day accuracy (98% to 102%) and inter-day precision (0.9% to 3.5% CV) when applied to applesauce-exposed PERTZYE EC microspheres. Additionally, the inter-day accuracy for the applesauce-exposed microsphere was estimated to be 98-105%.

### **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%.

### 3 DETAILED LABELING RECOMMENDATIONS

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



(b) (4)

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

## 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 PERTZYE 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

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.

**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 |
|-----------------------------------|--------|--------|---------|---------|---------|---------|
| <b>Lipase Activity (USP U/mg)</b> |        |        |         |         |         |         |
| 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 |
|-----------------------------------|--------|--------|---------|---------|---------|---------|
| <b>Lipase Activity (USP U/mg)</b> |        |        |         |         |         |         |
| 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    |

**Reviewer Comment:**

*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 (*

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)<sup>a</sup>**

| Concentration              | 6<br>U/mL   | 8<br>U/mL   | 10<br>U/mL  | 12<br>U/mL  | 14<br>U/mL  | 16<br>U/mL  |
|----------------------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Lipase Activity (USP U/mg) |             |             |             |             |             |             |
| Day 1,<br>Replicate 1      | 32.36       | 30.46       | 29.64       | 29.55       | 27.61       | 27.46       |
| Day 1,<br>Replicate 2      | 32.49       | 29.21       | 28.76       | 29.67       | 26.78       | 27.64       |
| Day 2,<br>Replicate 1      | 32.61       | 30.25       | 30.91       | 29.52       | 27.60       | 27.08       |
| Day 2,<br>Replicate 2      | 32.18       | 30.93       | 29.94       | 29.50       | 27.63       | 26.67       |
| Day 3,<br>Replicate 1      | 32.57       | 31.84       | 30.54       | 30.23       | 29.09       | 28.19       |
| Day 3,<br>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<br>Value*        | 31.8        | 30.4        | 29.4        | 29.1        | 27.8        | 27.3        |
| <b>Day 1<br/>Accuracy</b>  | <b>102%</b> | <b>98%</b>  | <b>99%</b>  | <b>102%</b> | <b>98%</b>  | <b>101%</b> |
| <b>Day 2<br/>Accuracy</b>  | <b>102%</b> | <b>101%</b> | <b>103%</b> | <b>101%</b> | <b>99%</b>  | <b>98%</b>  |
| <b>Day 3<br/>Accuracy</b>  | <b>105%</b> | <b>105%</b> | <b>104%</b> | <b>103%</b> | <b>104%</b> | <b>102%</b> |

\*Calculated mean lipase activity for QC samples (see Table 2)

<sup>a</sup> 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

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

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:

**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 |
|--|--------------------------------------|----------------------------|--|---|
| <b>MS-16 Lot PC-11H06B-16-01 (Capsule Fill Weight = 549mg)</b> |                                      |                            |  |   |
| 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  |
| <b>MS-16 Lot PC-11H07B-16-01 (Capsule Fill Weight = 542mg)</b> |                                      |                            |  |   |
| 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  |
| <b>MS-16 Lot PC-11I08B-16-01 (Capsule Fill Weight = 549mg)</b> |                                      |                            |  |   |
| 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 | = | $\left( \frac{\text{Total lipase activity of the applesauce exposed microspheres}}{\text{Total lipase activity of the QC microsphere without applesauce exposure}} \right) \times 100$ |
|--|---|--|

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

**Table 8 – Comparative % Lipase Activity Recovered**

| Sample Number                    | QC Sample<br>Lipase Activity<br>(USP u/mg) | After 20 Min.<br>Applesauce<br>Exposure<br>Lipase Activity<br>(USP u/mg) | After 20 Min.<br>Applesauce<br>Exposure<br>Comparative %<br>Lipase Activity<br>Recovered |
|----------------------------------|--|--|--|
| <b>MS-16 Lot PC-11H06B-16-01</b> |  |  |  |
| 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  |
| <b>MS-16 Lot PC-11H07B-16-01</b> |  |  |  |
| 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  |
| <b>MS-16 Lot PC-11H08B-16-01</b> |  |  |  |
| 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)."*

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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DIONNA J GREEN  
04/20/2012

YOW-MING C WANG  
04/20/2012