

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022523Orig1s000**

**CHEMISTRY REVIEW(S)**



**DATE:** March 23, 2010

**FROM:** Howard Anderson, Ph.D. Biologist, DTP/OBP/OPS/CDER

**THROUGH:** Emanuela Lacana, PhD, Associate Chief Laboratory of Chemistry  
Barry Cherney, PhD, Deputy Directory Division of Therapeutic Proteins

**SUBJECT:** Executive Product Quality Summary

**NDA:** 22-523

**SPONSOR:** Johnson & Johnson

**DRUG PRODUCT:** Pancreaze (Pancrelipase Delayed Release Capsules)

**API/DRUG SUBSTANCE:** DMF 7090

**OND/ODE III:** Division of Gastroenterology Products

**RPM:** Stacey Barley

## The Chemistry Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The Division of Therapeutic Proteins, Office of Biotechnology Products, OPS, CDER, recommends approval of NDA #22-523 for PANCREAZE, (pancrelipase) manufactured by Johnson & Johnson (J&J) Pharmaceuticals. The data submitted in this application support the conclusion that the manufacture of pancrelipase is controlled, and leads to a product that is consistent and potent. The conditions used in manufacturing have been validated, and a consistent product is produced by the process. It is recommended that this product be approved for human use (under conditions specified in the package insert).

Although some lots of pancrelipase have been shown to contain infectious porcine parvovirus (PPV), the risk that PPV can cross species and transmit diseases to humans is minimal, and is outweighed by the clinical benefit provided by pancrelipase.

**B. Recommendation on Post-Marketing Commitments (PMC)**

On page 6 of this review are the PMCs that should be addressed. They concern the drug substance label, improving viral detection assays and surveillance strategies during manufacturing of the drug substance, reevaluation and potential adjustment to acceptance criteria for the drug product amylase and protease potency assays, and a stability study to confirm stability of Pancreaze under conditions of use.

## II. Summary of Chemistry Assessments

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

- General: Pancrelipase is the USAN name for the active pharmaceutical ingredient in Pancreaze<sup>®</sup>, and is a complex mixture of proteins obtained from porcine pancreas. Pancrelipase contains amylase, lipase, and colipase, (b) (4) and several proteases, including (b) (4) as well as many other proteins.
- Complexity: As described above, the product is a complex mixture of different proteins present in the pancreatic extracts. The pancreatic extracts have been characterized based upon their enzymatic activities, and by using analytical techniques such as Isoelectric focusing, SDS-PAGE, Reverse-Phase HPLC and by two dimensional SDS-PAGE. Protein sequencing and Mass Spectrometry were employed to identify RP-HPLC peaks and 2D-SDS-PAGE spots, respectively.
- Biological activity: Pancrelipase functions to replace pancreatic enzymes, absent in patients with cystic fibrosis or pancreatic insufficiencies. The enzymes contained in pancrelipase are active in the intestinal environment, where they contribute to the digestion of fats, starch and proteins in food. Lipase, amylase and proteases are all considered active ingredients in pancrelipase. However, clinical efficacy has been demonstrated only for lipase. Lipase requires colipase as a cofactor in a 1:1 ratio for full enzymatic activity. Colipase facilitates lipid substrate access and presentation to lipase. In its absence lipase activity is reduced. Nordmark (DMF 7090) has demonstrated that colipase is consistently in excess in all the 24 batches of pancrelipase tested. Therefore, lipase activity is not restricted by limiting amounts of colipase and is consistent from batch to batch of pancrelipase.
- Potency Assays to Measure Activity. Three assays are used to assess pancrelipase potency and these assays measure lipase, amylase and protease activities. All assays are based on established USP methods. Enzymatic assays measure the conversion of a specific enzyme substrate into a product. The substrate used in the lipase assay is olive oil. The triglycerides contained in the olive oil are hydrolyzed to free fatty acids, and the enzymatic activity is

measured by sodium hydroxide titration of the free fatty acids generated. Lipase activity is calculated by comparing the rate of olive oil hydrolysis by the drug substance to the rate of olive oil hydrolysis by a USP pancrelipase reference standard. Starch is the substrate used in the amylase activity assay. Starch reacts strongly with iodine, turning a deep blue color. Digestion of starch by amylase is measured as reduction in color intensity and the amylase activity is measured by comparing the starch hydrolysis rate by the drug substance or product to the starch hydrolysis rate by a USP pancrelipase reference standard. Protease potency is measured using casein as a substrate. Casein digestion by protease generates peptides that are soluble after acid treatment of the reaction mixture, in contrast to casein protein, which precipitates out of solution instead. The precipitated casein is removed by filtration and the amount of soluble peptides is quantified by absorbance at 280 nm. Protease activity is calculated by comparing the casein hydrolysis rate by the drug substance or product to the casein hydrolysis rate by a USP pancrelipase reference standard.

- Drug Product Presentation: Pancreaze<sup>®</sup> is administered orally in gelatin capsules. It is presented in four strengths, based on the lipase activity content: 4,200, 10,500, 16,800, and 21,000 USP lipase units (100 per bottle). Each capsule contains enteric coated pancrelipase micro tablets (MT). The capsules are packaged in amber glass bottles. Only the 4,200 USP lipase unit bottles contains a desiccant package because the capsules contain more air space. Air contains moisture and on during storage moisture makes the product less stable....
- Excipient: Pancreaze<sup>®</sup> is formulated with microcrystalline cellulose (b) (4), crospovidone (b) (4), colloidal anhydrous silica (b) (4), (b) (4), magnesium stearate (b) (4), (b) (4), (b) (4), triethyl citrate, talc, simethicone emulsion, montan glycol wax).
- Drug Substance and Product Manufacture: Pancrelipase drug substance is manufactured by processing of porcine pancreases. (b) (4)

(b) (4)

- Drug Substance Purity: The above process includes three steps that are relevant for viral inactivation: (b) (4). The source material is known to be contaminated by endogenous viruses and infectivity assays are performed on drug substance at release, to monitor for viral levels. Infectious PPV was detected in approximately 50% of the pancrelipase batches analyzed. The risk that PPV crosses species and infects humans is considered minimal and is outweighed by the clinical benefit provided by pancrelipase. PCV1 and PCV2 genome equivalents have also been detected in the drug substance. Infectious PCV2 has been detected in the drug substance and a specification has been established to monitor and control for the viral levels. An infectious assay for PCV1 is not available and the sponsor has agreed to develop and validate an assay for lot release. 60 lots of drug substance have tested negative for HEV, PEV 9 (SVDV), EMCV, Reo virus, and Rota A virus genome equivalents. However, the current assay sensitivity needs to be improved to ensure material contaminated with porcine viruses with the potential to infect humans is rejected. This issue will be addressed with Post-Marketing Commitments.
- Drug Substance and Product Release Tests:  
The release tests for drug substance include: appearance, identity by enzyme activity (lipase, protease and amylase), RP-HPLC (product and process related impurities), water, residual solvents, loss on drying, fat content, microbial testing. Potency is measured by enzyme activity (lipase, protease and amylase). Drug product testing includes, in addition to the drug substance assays described above: water content (loss on drying) of pellets, particle size, mean weight of pellet/capsule, disintegration of capsules and dissolution of pancrelipase pellets.

### **Critical Product Attributes**

- i. **Lipase activity:** Lipase activity is a critical product attribute linked to both safety and efficacy. Excessive consumption of lipase has been correlated to fibrosing colonopathy in children younger than 12 years of age. The primary efficacy endpoint in clinical studies was the Coefficient of Fat Absorption, which is surrogate for lipase activity.
- ii. **Moisture:** Pancrelipase is sensitive to moisture: lipase activity is quickly lost upon exposure to moisture due to activation of protease activity which degrades lipase.

- iii. Dissolution: Dissolution of microtablets is essential for protection of the lipase contained in Pancreaze in the stomach and release of pancreatic enzymes in the intestine. The small intestine is where Pancreaze is intended to carry out its therapeutic action.
- iv. Microbial and viral content: Tests performed on the drug substance and drug product to ensure microbial control include: total aerobic microbial count, total combined yeasts and mold counts, and absence of Salmonella and Escherichia coli . Extensive viral testing is also included in the drug substance release program.

### **III. Regulatory History**

NDA 22-523 is an original submission. However the drug substance (DMF 7090) used to produce Pancreaze has an extensive regulatory history. The Zenpep NDA 22-210 (submitted by EURAND a different manufacturer), approved by FDA in August 2009, also uses the same drug substance. NDA 22-210 was originally submitted on December 17, 2007. The ZenPep pancrelipase drug product is manufactured using a pancrelipase drug substance manufactured by Nordmark. The information for the drug substance product quality is provided in DMF 7090. Dr. Anderson was the primary reviewer for all product quality sections in the DMF, except those concerning viral issues. Dr. Ennan Guan reviewed all viral issues. The original review identified deficiencies and on the PUDFA date (June 17, 2008) a letter was sent to Nordmark listing all product quality deficiencies.

The deficiencies associated with the manufacture of the drug substance included;

- A risk mitigation plan for controlling potential adventitious agents.
- Performing viral spiking studies to evaluate the manufacturing process capacity to inactivate adventitious agents.
- The validation of qPCR and infectivity assays to monitor for viral adventitious agents.
- The establishment of appropriate acceptance criteria for viral lot release assays.
- The demonstration of control of colipase activity to ensure pancrelipase potency consistency.
- The establishment of appropriate acceptance criteria for the HPLC identity test.
- The reference standard qualification program.
- The inclusion of an expiry on the drug substance label.

### **IV Regulatory Basis for Approvability**

NDA 22-210 and DMF 7090 were updated on December 22, 2008, in the sponsor's complete response to start the second review cycle. Dr. Anderson was the primary reviewer for the recently submitted CMC information requests, including those involving viral issues. During this review period the DMF was updated on March 31, 2009, and May 18, 2009. Eurand and Nordmark have adequately addressed all issues raised in the DTP approvable letter (now called complete response letter). NDA 22-210 was approved in August 2009 with post marketing commitments to address NDA and DMF deficiencies. The manufacture of the Pancreaze product is of a similar quality standard to the ZenPep and Creon. The Creon pancreatic enzyme product

was approved by the FDA in April, 2009. Pancreaze is manufactured by a process that contains steps aimed at greatly reducing enveloped viral infections agents in the source material. The Pancreaze manufacturing process results in a pancrelipase drug product that is representative of the label claim and should be approved for the proposed indication.

The Nordmark facility was inspected in April 2009, by Dr. Anderson (DTP/OPS) and Gwyn Dickinson (ORA/DFI) for cGMP compliance for manufacture of the pancrelipase drug substance (DMF 7090). The inspection resulted in seven 483 observations. Nordmark's response to the 483 items was found to be adequate, and FDA found the facility adequate and recommended approval the Zenpep product (NDA 22-210). Nordmark was inspected by ORA for manufacture of the Pancreaze drug product in February 2010, and no major deficiencies were identified. CDER/OC recommended approval of the facility for manufacture of the Pancreaze Drug Product on March 23, 2010.

## **Post Marketing Commitments**

### **Drug Product**

1. Initiate and complete the proposed studies ( Protocol #s 04020298 & 04020299) that evaluate the stability of Pancreaze under conditions of use.
2. Re-evaluate the acceptance criteria for the protease and amylase assays after more experience is gained with the PANCREAZE manufacturing process. After 50 lots of low-potency microtablets and 25 lots of high-potency microtablets are manufactured, specifications will be re-evaluated and adjusted to reflect manufacturing history and capability.

### **Drug Substance**

3. Develop and validate an infectious assay for PCV1.
4. Establish lot release specifications for PCV1.
5. Perform additional monitoring of viral load entering the manufacturing process. The control program will include monitoring for human pathogenic viruses by qPCR. An appropriate control strategy will then be implemented.
6. Improve the sensitivity of the qPCR assays used for drug substance release testing in order to provide adequate assurance that released drug substance will not contain EMCV, HEV, PEV-9, Reo1/3, Rota, Influenza, VSV-IND, and VSV-NJ viruses. Revise the assays, and submit assay validation data, together with acceptance criteria.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22523	ORIG-1	JOHNSON & JOHNSON PHARMACEUTICA L RESEARCH & DEVELOPMENT LLC	Pancrelipase Microtablets

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/s/

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HOWARD A ANDERSON  
04/12/2010

EMANUELA LACANA  
04/12/2010

BARRY W CHERNEY  
04/12/2010



**March 23, 2009**

**NDA #:** 22-523  
**PRODUCT NAME:** Pancreaze MT

**SUBMISSION DATE:** June 23, 2009  
**FILING DATE:** November 23, 2009  
**PDUFA GOAL DATE:** April 23, 2010

**FROM:** Howard Anderson, PhD, Biologist  
**THROUGH:** Emanuela Lacana, PhD, Associate Chief Laboratory of Chemistry.  
Gibbes Johnson, PhD, Chief Laboratory of Chemistry  
Barry Cherney, PhD, Deputy Directory Division of Therapeutic Proteins  
**SUBJECT:** Product Quality Review of NDA 22-523 Drug Product

**PRODUCT:** Pancreatic Enzyme Product (PEP)  
Delayed-Release Capsules  
4,200, 10,500, 16,800 & 21,000 Lipase U USP/capsule

**INDICATION:** Exocrine Pancreatic Insufficiency for Cystic Fibrosis and Chronic Pancreatitis

**ROUTE OF ADMIN:** Oral  
**SPONSOR:** Johnson & Johnson Pharmaceutical Research & Development, LLC  
920 Route 202 South  
Raritan, NJ 08869  
Ilona J. Scott, Director, CNS/IM Global Regulatory Affairs

**CLINICAL DIVISION:** Division of Gastroenterology Products

**RPM:** Stacy Barley, 301-796-213

**RECOMMENDATION:** I recommend approval of this NDA with the post marketing commitments provided on page 3 of this review. The product quality standard for Pancreaze is equivalent to the recently FDA approved Creon and Zenpep pancreatic enzyme products.

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## Summary

The Pancreaze drug substance and drug product are manufactured by Nordmark and Johnson & Johnson (J&J) is responsible for the distribution and marketing of the product. This product class, pancreatic enzyme proteins (PEPs), is manufactured by a process that involves (b) (4)

. The drug product production involves the generation of micro-tablets which are filled into gelatin capsules. Two similar PEPs have recently been approved by the FDA and are manufactured by a similar process. The Creon drug substance and product are manufactured by Solvay Pharmaceuticals. The Zenpep drug substance is manufactured by Nordmark and the drug product is manufactured by Eurand. The Creon NDA (20725) was approved in April 2009, and the Zenpep NDA (22210) was approved in August 2009).

The Zenpep and Pancreaze drug substance manufacturing process is identical (DMF 7090). DMF 7090 was reviewed by Dr. Howard Anderson of the Division of Therapeutic Proteins and found to be sufficient to support the approval of Zenpep. An extensive evaluation of the drug substance quality is located the DMF 7090 review.

This review contains an evaluation of Pancreaze drug product quality. Provided in this review is a summary of the product quality information provided in the NDA in eCTD format. Dr. Anderson's evaluation of the information is located in italic font throughout the application. It should be noted that during this review two information requests (IR) were sent to J&J to address deficiencies in the application. The responses adequately addressed the concerns.

The product quality standard for Pancreaze is equivalent to or exceeds that the Zenpep product. In particular, the Pancreaze drug product production involves a (b) (4) step. The Zenpep drug product process does not have an (b) (4). The (b) (4) offers an additional viral and microbial reduction or inactivation step that will further minimize the risk of contamination of the Pancreaze product with these agents. Deficiencies were identified during the primary review. They do not however, preclude approval of the application since the majority were addressed by information requests during the review cycle and the remaining pending issues can be addressed as post-marketing commitments (PMCs). PMCs are located in the next section of this review. It should be noted that most of these post marketing commitments also exist for the Zenpep product.

## Post Marketing Commitments:

### Drug Product

1. Initiate and complete the proposed studies (Protocol #s 04020298 & 04020299) that evaluate the stability of Pancreaze under conditions of use.
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**CATEGORICAL ENVIRONMENTAL EXCLUSION**

In the US Regional Section of the NDA the sponsor has requested categorical exclusion from an environmental assessment. I recommend approval of this request since this application involves "biologic" substances, pancreatic enzymes, which occur naturally in the environment as describe in FDA Guidance Environmental Assessment of Human Drug and Biologics Applications. Approval of this NDA will not alter significantly the concentration or distribution of the substance or its degradation products in the environment based on regulations established in part 21 CFR 25.31 (c).

**DRUG MASTER FILES CROSS REFERENCED:**

Letters of Authorization have been provided for the following DMFs

DMF 7090 Pancrelipase DS: Nordmark

(b) (4)



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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22523	ORIG-1	JOHNSON & JOHNSON PHARMACEUTICA L RESEARCH & DEVELOPMENT LLC	Pancrelipase Microtablets

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