

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022523Orig1s000

OTHER REVIEW(S)



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

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

Memorandum

PROJECT MANAGER'S REVIEW

Application Number: NDA 22-523

Name of Drug: PANCREAZE™ (Pancrelipase Capsules)

Sponsor: Johnson and Johnson Pharmaceutical Research & Development, L.L.C.

Material Reviewed: PANCREAZE™ (Pancrelipase) Delayed-Release Capsules
Carton and Container Labels

OBP Receipt Date: June 23, 2009, November 19, 2009, April 7, 2010

EXECUTIVE SUMMARY

The carton and container labels for PANCREAZE™ (Pancrelipase) Delayed-Release Capsules were reviewed and found to comply with the following regulations : 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 200.100 and United States Pharmacopoeia, 12/1/09-5/1/10, USP 32/NF 27. Labeling deficiencies were identified and mitigated. Please see comments in the conclusions section. The revised carton and container labels are acceptable.

Background:

PANCREAZE™ (Pancrelipase) Delayed-Release Capsules is a New Drug Application (NDA) indicated as a combination of porcine-derived lipases, proteases, and amylases indicated for the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions.

Labels Reviewed:

PANCREAZE® (Pancrelipase) Container Label
4,200 Lipase Units -100 ct Trade Bottle
21,000 Lipase Units -100 ct Trade Bottle

16,800 Lipase Units -100 ct Trade Bottle

10,500 Lipase Units -100 ct Trade Bottle

PANCREAZE® (Pancrelipase) Carton Label

4,200 Lipase Units -100 ct Trade Bottle

21,000 Lipase Units -100 ct Trade Bottle

16,800 Lipase Units -100 ct Trade Bottle

10,500 Lipase Units -100 ct Trade Bottle

Review

The carton and container labels for PANCREAZE® (Pancrelipase) were reviewed using the following regulations: 21 CFR 201.1 through 21 CFR 201.18; 21 CFR 201.25; and 21 CFR 201.50 through 21 CFR 201.55 through 21 CFR 200.57; 21 CFR 201.100 and United States Pharmacopeia, 12/1/10-5/1/10, USP 32/NF27. Please see comments in the conclusions section.

I. Container

A. Bottle Label

1. 21 CFR 201.1 Drugs; name and place of business of manufacturer, packer or distributor-
Manufactured By: Nordmark Arzneimittel GmbH & Co. KG
25436 Uetersen, Germany
Manufactured for: McNeil Pediatrics, Division of Ortho-McNeil-Jansen Pharmaceuticals, Inc. Titusville, NJ 08560
This conforms to the regulation.
2. 21 CFR 201.2 Drugs and devices; National Drug Code numbers-
The National Drug Code (NDC) number is located above the proprietary name at the top of the label. It is noted as NDC 50458-XXX-60. The NDC number conforms to 21 CFR 207.35 as a 3-2 Product-Package Code configuration. This conforms to the regulation.
3. 21 CFR 201.5 Drugs; adequate directions for use-On the left of the label “For dosage and other prescribing information, see accompanying product literature.” appears on the container labels. This conforms to the regulation.
4. 21 CFR 201.6 Drugs; misleading statements- The proprietary name PANCREAZE™ appears on the label with the established name, pancrelipase. This conforms to the regulation.
5. 21 CFR 201.10 Drugs; statement of ingredients- The established

name, Pancrelipase is not used in type at least half as large as the most prominent presentation of the proprietary name, PANCREAZE®. **This does not conform to the regulation.**

6. 21 CFR 201.15 Drugs; prominence of required label statements- All required statements (“Rx Only” and “Protect from Moisture”) appear on the label. “Protect from Moisture” and “Avoid excessive heat” do not appear on the label. **This does not conform to the regulation.**
7. 21 CFR 201.17 Drugs: location of expiration date-The expiration date appears under the lot identification number on the right side of the label. This conforms to the regulation.
8. 21 CFR 201.25 Bar code label requirements – The bar code is located on the left of the label with sufficient white space surrounding to ensure for proper scanning. This conforms to the regulation.
9. 21 CFR 201.50 Statement of identity- The ingredients, Lipase, Amylase and Protease are listed with corresponding units per capsule per 21 CFR 201.10. This conforms to the regulation.
10. 21 CFR 201.51 Declaration of net quantity of contents – The label prominently states the net quantity of contents in terms of numerical count in units on the label, below the proprietary and established name. This conforms to the regulation.
11. 21 CFR 201.55 Statement of dosage- On the left of the label “For dosage and other prescribing information, see accompanying product literature.” appears on the container labels. This conforms to the regulation.
12. 21 CFR 201.100 Prescription drugs for human use- The label bears statements “Rx Only”, identifying lot number, storage conditions and a reference to the package insert. “Protect from Moisture” and “Avoid excessive heat” are not listed on the label. **This does not conform to the regulation.**
13. 21 CFR 208.24 Distribution and dispensing of a Medication guide- If a Medication Guide is required under part 208 of chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label. This conforms to the regulation.

II. Carton

1. 21 CFR 201.1 Drugs; name and place of business of manufacturer, packer, or distributor- The label states:
Manufactured By: Nordmark Arzneimittel GmbH & Co. KG
25436 Uetersen, Germany
Manufactured for: McNeil Pediatrics, Division of Ortho-McNeil-Jansen Pharmaceuticals, Inc. Titusville, NJ 08560
This conforms to the regulation.
2. 21 CFR 201.2 Drugs and devices; National Drug Code numbers-
The National Drug Code (NDC) number is located above the proprietary name at the top of the label. It is noted as NDC 50458-XXX-60. The NDC number conforms to 21 CFR 207.35 as a 3-2 Product-Package Code configuration. This conforms to the regulation.
3. 21 CFR 201.5 Drugs; adequate directions for use-On the left of the label “For dosage and other prescribing information, see accompanying product literature.” appears on the container labels. This conforms to the regulation.
4. 21 CFR 201.6 Drugs; misleading statements - The proprietary name, PANCREAZE™ appears with the established name, pancrelipase on the carton. This conforms to the regulation.
5. 21 CFR 201.10 Drugs; statement of ingredients- The established name, Pancrelipase is not used in type at least half as large as the most prominent presentation of the proprietary name, PANCREAZE®. **This does not conform to the regulation.**

6. 21 CFR 201.15 Drugs; prominence of required label statements- All required statements (“Rx Only” and “Protect from Moisture” appear on the label. “Protect from Moisture” and “Avoid excessive heat” do not appear on the label. **This does not conform to the regulation.**
7. 21 CFR 201.17 Drugs; location of expiration date - The expiration date appears on the carton below the lot number. This conforms to the regulation.
8. 21 CFR 201.25 Bar code label requirements - The bar code is located at the bottom of the back panel of the carton with sufficient white space surrounding to ensure for proper scanning. This conforms to the regulation.
9. 21 CFR 201.50 Statement of identity - The ingredients, Lipase, Amylase and Protease are listed with corresponding units per capsule per 21 CFR 201.10. This conforms to the regulation.
10. 21 CFR 201.51 Declaration of net quantity of contents - The label does state the net quantity of contents in terms of numerical count in units at the top of the carton. This conforms to the regulation.
11. 21 CFR 201.55 Statement of dosage - The label states “For dosage and other prescribing information, see accompanying product literature. This conforms to the regulation.
12. 21 CFR 201.100 Prescription drugs for human use - The label bears statements for “Rx Only”, an identifying lot number, storage conditions, and a reference to the package insert. “Protect from Moisture” and “Avoid excessive heat” are not listed on the label. **This does not conform to the regulation.**
13. 21 CFR 208.24 Distribution and dispensing of a Medication guide- If a Medication Guide is required under part 208 of chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label. This conforms to the regulation.

III. National Stock Number

1. Discussed the presentation of the NSN with the Chief of Quality of Assurance, Health and Human Services Supply Service Center, Program Support Center, Perry Point, Annette Quinones, 410-642-1386 on March 26, 2010 (NSN) 6505-01-287-2XXX, listed on the

container and carton labels for commercial use. Ms. Quinones informed me that the NSN is an internal government identification that is used on prescription products that are repackaged at Perry Point for government institutional use. The NSN number should be omitted from commercial prescription drug product labels.

Labels submitted November 19, 2009



(b) (4)

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Labels submitted April 6, 2010
Container labels

7
NDC 50458-341-60
For dosage and other prescribing information, see accompanying product literature. Keep out of reach of children.

PANCREAZE™
(pancrelipase)
Delayed-Release Capsules

Each capsule contains:
Lipase 4,200 USP Units
Amylase 17,500 USP Units
Protease 10,000 USP Units

DOSE BY LIPASE UNITS
Attention Pharmacist: Dispense the accompanying Medication Guide to each patient.

100 capsules

LOT:
EXP:

Each capsule contains enteric coated pancrelipase microtablets.
To protect enteric coating, microtablets should not be crushed or chewed.
Avoid heat. PANCREAZE™ hard gelatin capsules should be stored in a dry place in the original container. After opening, KEEP THE CONTAINER TIGHTLY CLOSED between uses to PROTECT FROM MOISTURE, Do not store above 25°C (77°F).
Manufactured by: Nordmark Arzneimittel GmbH & Co. KG
25436 Uetersen, Germany
Manufactured for: McNeil Pediatrics,
Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

Rx only.
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AW_53109

N0050946 100 1

3
50458-341-60
N

4
N 3 50458-342-60

For dosage and other prescribing information, see accompanying product literature. Keep out of reach of children.

NDC 50458-342-60

PANCREAZE™
(pancrelipase)
Delayed-Release Capsules

Each capsule contains:
Lipase 10,500 USP Units
Amylase 43,750 USP Units
Protease 25,000 USP Units

DOSE BY LIPASE UNITS
Attention Pharmacist: Dispense the accompanying Medication Guide to each patient.

100 capsules

LOT:
EXP:

Each capsule contains enteric coated pancrelipase microtablets.
To protect enteric coating, microtablets should not be crushed or chewed.
Avoid heat. PANCREAZE™ hard gelatin capsules should be stored in a dry place in the original container. After opening, KEEP THE CONTAINER TIGHTLY CLOSED between uses to PROTECT FROM MOISTURE. Do not store above 25°C (77°F).
Manufactured by: Nordmark Arzneimittel GmbH & Co. KG 25436 Uetersen, Germany
Manufactured for: McNeil Pediatrics, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc. Titusville, NJ 08560

Rx only.
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AW_53110

N0050947 103 1

1
N 3 50458-343-60

For dosage and other prescribing information, see accompanying product literature. Keep out of reach of children.

NDC 50458-343-60

PANCREAZE™
(pancrelipase)
Delayed-Release Capsules

Each capsule contains:
Lipase 16,800 USP Units
Amylase 70,000 USP Units
Protease 40,000 USP Units

DOSE BY LIPASE UNITS
Attention Pharmacist: Dispense the accompanying Medication Guide to each patient.

100 capsules

LOT:
EXP:

Each capsule contains enteric coated pancrelipase microtablets.
To protect enteric coating, microtablets should not be crushed or chewed.
Avoid heat. PANCREAZE™ hard gelatin capsules should be stored in a dry place in the original container. After opening, KEEP THE CONTAINER TIGHTLY CLOSED between uses to PROTECT FROM MOISTURE. Do not store above 25°C (77°F).
Manufactured by: Nordmark Arzneimittel GmbH & Co. KG 25436 Uetersen, Germany
Manufactured for: McNeil Pediatrics, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc. Titusville, NJ 08560

Rx only.
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AW_53111

N0050948 106 1

2
N 3 50458-346-60

For dosage and other prescribing information, see accompanying product literature. Keep out of reach of children.

NDC 50458-346-60

PANCREAZE™
(pancrelipase)
Delayed-Release Capsules

Each capsule contains:
Lipase 21,000 USP Units
Amylase 61,000 USP Units
Protease 37,000 USP Units

DOSE BY LIPASE UNITS
Attention Pharmacist: Dispense the accompanying Medication Guide to each patient.

100 capsules

LOT:
EXP:

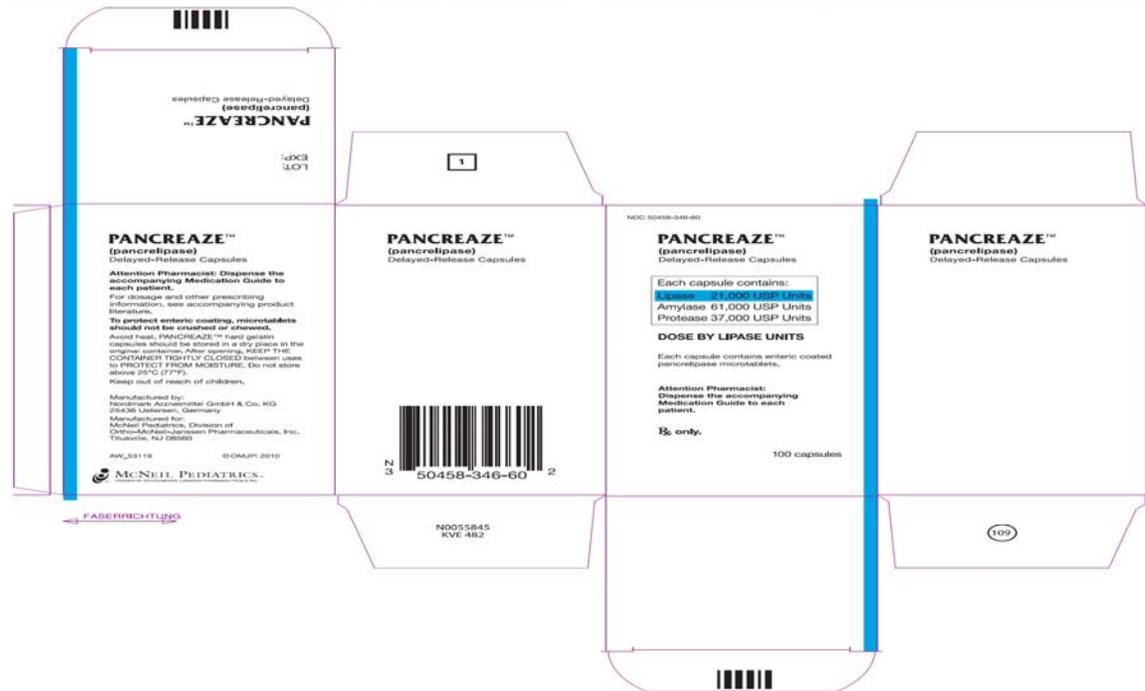
Each capsule contains enteric coated pancrelipase microtablets.
To protect enteric coating, microtablets should not be crushed or chewed.
Avoid heat. PANCREAZE™ hard gelatin capsules should be stored in a dry place in the original container. After opening, KEEP THE CONTAINER TIGHTLY CLOSED between uses to PROTECT FROM MOISTURE. Do not store above 25°C (77°F).
Manufactured by: Nordmark Arzneimittel GmbH & Co. KG 25436 Uetersen, Germany
Manufactured for: McNeil Pediatrics, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc. Titusville, NJ 08560

Rx only.
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AW_53112

N0050949 109 1

Cartons





III. Conclusions

- A. The proposed carton and container labeling are acceptable only upon the following changes:
1. Per 21 CFR 201.10, please revise the presentation of the established name and proprietary name. The established name shall have the prominence commensurate with the prominence of the proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features. It shall also be printed in letters that are at least half as large as the letters comprising proprietary name. **Change made and acceptable.**
 2. Per 21 CFR 201.15 and 21 CFR 201.100 - Please add the bolded statements, "Protect from moisture" and "Avoid excessive heat" to the storage conditions listed. **The statements "After opening, KEEP THE CONTAINER TIGHTLY CLOSED between uses to PROTECT FROM MOISTURE" and "Avoid heat" were added to the carton and container. Change acceptable.**
 3. Per Health and Human Services Supply Service Center, Perry Point, Maryland, please omit National Stock Numbers (NSN) from the carton and container labels. **Change made and acceptable.**
 4. Additional revisions that are acceptable are as follows:
 - a) A box was added to enclose the enzymes and corresponding Units.
 - b) "DOSE BY LIPASE UNITS" was added directly under the box listing the enzymes and corresponding Units.
 - c) The additional medication guide statement was removed from the side panel to the primary panel
 - d) The distinguishing color for Lipase 16,800, Amylase 70,000, and Protease 40,000 was changed from an orange hue to a teal hue.

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

Comment/Concurrence:

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

Barry Cherney, Ph.D.
Deputy Director
Division of Therapeutic Proteins
CDER/OPS/OBP

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

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

/s/

KIMBERLY M RAINS
04/09/2010

HOWARD A ANDERSON
04/12/2010

BARRY W CHERNEY
04/12/2010

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Title: Deferred requirement for development of an age appropriate formulation for PANCREAZE (pancrelipase) Delayed-Release Capsules to allow for dosing to the youngest, lowest weight pediatric patients, including infants less than 12 months of age who will be administered 2,000 to 4,000 lipase units per 120 mL of formula or per breast-feeding. Submit a supplement for an age appropriate formulation by October, 2012.

| | | |
|------------------------------|-------------------------------------|-------------------|
| PMR/PMC Schedule Milestones: | Protocol Submission Date: | <u>MM/DD/YYYY</u> |
| | Study Initiation Date: | <u>MM/DD/YYYY</u> |
| | Study Completion Date: | <u>MM/DD/YYYY</u> |
| | Final Study Report Submission Date: | <u>MM/DD/YYYY</u> |
| | Other: _____ | <u>MM/DD/YYYY</u> |

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

The low weight pediatric patients are a small subpopulation affected.

2. If required, characterize the **PMR**. Check all that apply and add text where indicated.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated approval
- Animal efficacy confirmatory studies
- Pediatric requirement
- FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

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

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**

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

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

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

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

4. If not required by regulation, characterize the review issue leading to this **PMC**

5. What type of study or clinical trial is required or agreed upon (describe)?

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

Required

- Pharmacoepidemiologic study (list risk to be evaluated)

- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)

- Subpopulation (list type)

- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study (provide explanation)

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

Agreed upon:

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

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

6. Is the PMR/PMC clear and feasible?

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:

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

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Title: A 10 year, observational study to prospectively evaluate the incidence of fibrosing colonopathy in patients with cystic fibrosis treated with PANCREAZE (pancrelipase) Delayed-Release Capsules in the US and to assess potential risk factors for the event.

PMR/PMC Schedule Milestones:

| | |
|-------------------------------------|----------------------|
| Protocol Submission Date: | <u>June, 2011</u> |
| Study Initiation Date: | <u>MM/DD/YYYY</u> |
| Study Completion Date: | <u>January, 2022</u> |
| Final Study Report Submission Date: | <u>August, 2022</u> |
| Other: _____ | <u>MM/DD/YYYY</u> |

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

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

2. If required, characterize the **PMR**. Check all that apply and add text where indicated.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated approval
- Animal efficacy confirmatory studies
- Pediatric requirement
- FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

In the drug class of Pancrelipase, there were cases of fibrosing colonopathy identified.

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

Fibrosing colonopathy is a serious, rare condition that has been described in association with high-dose pancreatic enzyme use.

- **If the PMR is a FDAAA safety study/clinical trial, does it:**

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

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

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

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

Fibrosing colonopathy has been reported following treatment with different pancreatic enzyme products. Fibrosing colonopathy is a rare, serious adverse reaction initially described in association with high-dose pancreatic enzyme use, usually over a prolonged period of time and most commonly reported in pediatric patients with cystic fibrosis.

4. If not required by regulation, characterize the review issue leading to this **PMC**

5. What type of study or clinical trial is required or agreed upon (describe)?

Required

- Pharmacoepidemiologic study (list risk to be evaluated)

- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)
 Fibrosing Colonopathy

- Subpopulation (list type)

- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study
 (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

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

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

6. Is the PMR/PMC clear and feasible?

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:

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

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Title: A 10 year, observational study to prospectively evaluate the risk of transmission of selected porcine viruses in patients taking PANCREAZE (pancrelipase) Delayed-Release Capsules

PMR/PMC Schedule Milestones:

| | |
|-------------------------------------|------------------------|
| Protocol Submission Date: | <u>June, 2011</u> |
| Study Initiation Date: | <u>MM/DD/YYYY</u> |
| Study Completion Date: | <u>December, 2021</u> |
| Final Study Report Submission Date: | <u>September, 2022</u> |
| Other: | <u>MM/DD/YYYY</u> |

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

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

2. If required, characterize the **PMR**. Check all that apply and add text where indicated.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated approval
- Animal efficacy confirmatory studies
- Pediatric requirement
- FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

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

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

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

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
 - Assess a known serious risk related to the use of the drug?
 - Assess signals of serious risk related to the use of the drug?
 - Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
 - Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

 - Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

 - Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

 - Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

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

4. If not required by regulation, characterize the review issue leading to this PMC

5. What type of study or clinical trial is required or agreed upon (describe)?

Required

- Pharmacoepidemiologic study (list risk to be evaluated)

- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)
Transmission of porcine viruses.

- Subpopulation (list type)

- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study
(provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

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

- Other
Ten year observational study to evaluate the risk of transmission of selected porcine viruses.

6. Is the PMR/PMC clear and feasible?

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:

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

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Title: Initiate and complete the proposed studies (Protocol #s 04020298 & 04020299) that evaluate the stability of Pancreaze under conditions of use.

PMR/PMC Schedule Milestones:

| | |
|-------------------------------------|--------------------------|
| Protocol Submission Date: | <u>MM/DD/YYYY</u> |
| Study Initiation Date: | <u>MM/DD/YYYY</u> |
| Study Completion Date: | <u>MM/DD/YYYY</u> |
| Final Study Report Submission Date: | <u>September,30,2011</u> |
| Other: | <u>_____</u> |

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

Johnson&Johnson did not conduct formal stability studies to evaluate the product under conditions of use, to simulate the opening and closing of the container that occurs when patients remove their medicine. In the NDA, the sponsor provided data to support the stability of the product at accelerated conditions (i.e. high temperatures and high humidity). Additionally, the instructions for use provided in the package insert and medication guide limit the risk of exposure of the product to conditions that might adversely affect stability. Therefore it is appropriate to conduct the study post-marketing.

2. If required, characterize the **PMR**. Check all that apply and add text where indicated.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated approval
- Animal efficacy confirmatory studies
- Pediatric requirement
- FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**

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

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

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

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

4. If not required by regulation, characterize the review issue leading to this **PMC**

A formal stability study evaluating the product under conditions of use has not been conducted and thus this information is not present in the original NDA submission. The sponsor has provided two study protocols that were reviewed and found to be acceptable. This study will be adequate to confirm that the product remains stable after being exposed to the ambient environment under worst case conditions. (b) (4)

5. What type of study or clinical trial is required or agreed upon (describe)?

Required

- Pharmacoeconomic study (list risk to be evaluated)

- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)

- Subpopulation (list type)

- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoeconomic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- Dose-response study performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

6. Is the PMR/PMC clear and feasible?

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:

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

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Title: 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.

PMR/PMC Schedule Milestones:

| | |
|-------------------------------------|-----------------------|
| Protocol Submission Date: | <u>MM/DD/YYYY</u> |
| Study Initiation Date: | <u>MM/DD/YYYY</u> |
| Study Completion Date: | <u>MM/DD/YYYY</u> |
| Final Study Report Submission Date: | <u>March 31, 2013</u> |
| Other: _____ | <u>MM/DD/YYYY</u> |

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

Johnson & Johnson has been manufacturing Pancreaze since 1988, and the process has not significantly changed. Johnson & Johnson however has only recently formally validated the process. The sponsor proposes a specification of (b) (4) %, but only 3 or 4 lots of testing results for the amylase and protease assays are provided in the NDA. There is thus not enough information in the NDA to establish acceptance criteria based on manufacturing history and capability. When Johnson & Johnson has a better understanding of process capability the amylase and protease potency specifications should be reevaluated, and adjusted to reflect process capability and be consistent with the activities of the product used in the clinical trial. This information can only be obtained through continued manufacturing so it is appropriate and indeed a typical post-marketing commitment for many applicants, due to the lack of extensive manufacturing history using the validated commercial process.

2. If required, characterize the **PMR**. Check all that apply and add text where indicated.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated approval
- Animal efficacy confirmatory studies
- Pediatric requirement
- FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**

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

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

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

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

4. If not required by regulation, characterize the review issue leading to this **PMC**

New manufacturing process controls have recently been developed to provide better assurance of drug product quality. Limited lots of material have been generated and it is thus difficult to establish acceptable limits for the amylase and protease assays while still ensuring product availability. This PMC is consistent with the concepts established in ICH Q6B, Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products. It is also a typical PMC for original approvals for protein products.

5. What type of study or clinical trial is required or agreed upon (describe)?

Required

- Pharmacoeconomic study (list risk to be evaluated)

- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)

- Subpopulation (list type)

- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoeconomic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- Dose-response study performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

6. Is the PMR/PMC clear and feasible?

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:

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

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Title: Develop and validate an infectious assay for PCV1.

| | | |
|------------------------------|-------------------------------------|-------------------------|
| PMR/PMC Schedule Milestones: | Protocol Submission Date: | <u>MM/DD/YYYY</u> |
| | Study Initiation Date: | <u>MM/DD/YYYY</u> |
| | Study Completion Date: | <u>MM/DD/YYYY</u> |
| | Final Study Report Submission Date: | <u>January 31, 2011</u> |
| | Other: _____ | <u>MM/DD/YYYY</u> |

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

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

2. If required, characterize the **PMR**. Check all that apply and add text where indicated.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated approval
- Animal efficacy confirmatory studies
- Pediatric requirement
- FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**

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

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

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

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

4. If not required by regulation, characterize the review issue leading to this **PMC**

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

5. What type of study or clinical trial is required or agreed upon (describe)?

| |
|----|
| NA |
|----|

Required

- Pharmacoeconomic study (list risk to be evaluated)

- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)

- Subpopulation (list type)

- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoeconomic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- Dose-response study performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

6. Is the PMR/PMC clear and feasible?

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:

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

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Title: Establish lot release specifications for PCV1 for the drug substance.

PMR/PMC Schedule Milestones:

| | |
|-------------------------------------|----------------------|
| Protocol Submission Date: | <u>MM/DD/YYYY</u> |
| Study Initiation Date: | <u>MM/DD/YYYY</u> |
| Study Completion Date: | <u>MM/DD/YYYY</u> |
| Final Study Report Submission Date: | <u>July 31, 2011</u> |
| Other: _____ | <u>MM/DD/YYYY</u> |

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

As stated in the previous PMC an infectious assay for PCV1 is not currently available as is going to be developed by Johnson&Johnson. After the assay is validated lot release specifications will be established for PCV1. Specifications will need to be established based on manufacturing history and capability. Thus this requirement can only be met as a PMC.

2. If required, characterize the **PMR**. Check all that apply and add text where indicated.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated approval
- Animal efficacy confirmatory studies
- Pediatric requirement
- FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
 - Assess a known serious risk related to the use of the drug?
 - Assess signals of serious risk related to the use of the drug?
 - Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
 - Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

 - Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

 - Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

 - Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

4. If not required by regulation, characterize the review issue leading to this **PMC**

ICH Q5A and the 2006 FDA PEP guidance have indicated that the pancrelipase manufacturing process should be robust to ensure removal of viral adventitious agents. PCV1 is a non enveloped virus and the PEP manufacturing process demonstrates no capability to inactivate non enveloped viruses. Therefore Johnson&Johnson should monitor for the virus and reject lots that contain high levels of the infectious agents.

5. What type of study or clinical trial is required or agreed upon (describe)?

Required

- Pharmacoepidemiologic study (list risk to be evaluated)

- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)

- Subpopulation (list type)

- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

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

- Other

6. Is the PMR/PMC clear and feasible?

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:

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

Attachment B: Sample PMR/PMC Development Template

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

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

| | | |
|------------------------------|-------------------------------------|----------------------|
| PMR/PMC Schedule Milestones: | Protocol Submission Date: | <u>MM/DD/YYYY</u> |
| | Study Initiation Date: | <u>MM/DD/YYYY</u> |
| | Study Completion Date: | <u>MM/DD/YYYY</u> |
| | Final Study Report Submission Date: | <u>July 31, 2011</u> |
| | Other: _____ | <u>MM/DD/YYYY</u> |

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

The current PCR assays sensitivity is sub optimal since the limit of detection is only 10 to 40 thousand genome equivalents per gram of drug substance which is beyond the capacity of the manufacturing process's ability to inactivate some viruses. While this is an important issue, availability of these products are critical and the risk to product quality has already been greatly reduced as compared to current marketed product. Again the risk is theoretical in that no infectious diseases are known to have been transmitted by the unapproved PEPs.

2. If required, characterize the **PMR**. Check all that apply and add text where indicated.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated approval
- Animal efficacy confirmatory studies
- Pediatric requirement
- FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**

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

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

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

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

4. If not required by regulation, characterize the review issue leading to this **PMC**

ICH Q5A and the 2006 FDA PEP guidance have indicated that the pancrelipase manufacturing process should be robust to ensure removal of viral adventitious agents. The manufacturing process demonstrates no capability to inactivate non enveloped viruses. Therefore, Johnson&Johnson should monitor for the virus with sensitive assays and reject lots that contain the infectious agents beyond the processes capacity to inactivate these viruses .

5. What type of study or clinical trial is required or agreed upon (describe)?

Required

- Pharmacoeconomic study (list risk to be evaluated)

- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)

- Subpopulation (list type)

- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoeconomic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- Dose-response study performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

6. Is the PMR/PMC clear and feasible?

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:

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

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Title: 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.

PMR/PMC Schedule Milestones:

| | |
|-------------------------------------|-------------------------|
| Protocol Submission Date: | <u>MM/DD/YYYY</u> |
| Study Initiation Date: | <u>MM/DD/YYYY</u> |
| Study Completion Date: | <u>MM/DD/YYYY</u> |
| Final Study Report Submission Date: | <u>January 31, 2011</u> |
| Other: _____ | <u>MM/DD/YYYY</u> |

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

The current PCR assays sensitivity is sub optimal since the limit of detection is only 10 to 40 thousand genome equivalents per gram of drug substance. The starting material for one lot is ^{(b) (4)} kg. Therefore, with the current assays, the sensitivity would be ^{(b) (4)} genome equivalent per lot. The assay sensitivity is equivalent for assays performed by different sponsors. All of these viruses have the potential to cause human infections, however based on the long history of use for these products, the risk of infections is low. This was a PMC for CREON and ZENPEP and should also be one for PANCREAZE.

2. If required, characterize the **PMR**. Check all that apply and add text where indicated.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated approval
- Animal efficacy confirmatory studies
- Pediatric requirement
- FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**

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

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

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

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

4. If not required by regulation, characterize the review issue leading to this **PMC**

ICH Q5A and the 2006 FDA PEP guidance have indicated that the pancrelipase manufacturing process should be robust to ensure removal of viral adventitious agents. The Nordmark process demonstrates no capability to inactivate non enveloped viruses. Therefore, Nordmark should monitor for the virus with sensitive assays and reject lots that contain the infectious agents. All of the virus in this PMC have the potential to cause human infections. This issue was addressed by PMC for both CREON and ZENPEP.

5. What type of study or clinical trial is required or agreed upon (describe)?

Required

- Pharmacoeconomic study (list risk to be evaluated)

- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)

- Subpopulation (list type)

- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoeconomic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- Dose-response study performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

6. Is the PMR/PMC clear and feasible?

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:

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

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Title: Perform *in vitro* studies to determine the feasibility of administering the contents of PANCREAZE (pancrelipase) Delayed-Release Capsules through a gastrostomy tube by December 30, 2010.

PMR/PMC Schedule Milestones:

| | |
|-------------------------------------|-------------------|
| Protocol Submission Date: | <u>MM/DD/YYYY</u> |
| Study Initiation Date: | <u>MM/DD/YYYY</u> |
| Study Completion Date: | <u>12/30/2010</u> |
| Final Study Report Submission Date: | <u>12/30/2010</u> |
| Other: _____ | <u>MM/DD/YYYY</u> |

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

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

2. If required, characterize the **PMR**. Check all that apply and add text where indicated.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated approval
- Animal efficacy confirmatory studies
- Pediatric requirement
- FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**

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

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

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

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

4. If not required by regulation, characterize the review issue leading to this **PMC**

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

5. What type of study or clinical trial is required or agreed upon (describe)?

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

Required

- Pharmacoepidemiologic study (list risk to be evaluated)

- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)

- Subpopulation (list type)

- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

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

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

6. Is the PMR/PMC clear and feasible?

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:

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

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

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

/s/

STACY R BARLEY
04/12/2010

ANIL K RAJPAL
04/12/2010

505(b)(2) ASSESSMENT

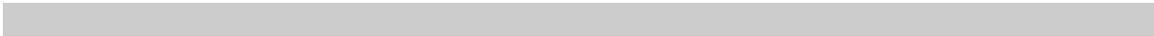
| Application Information | | |
|---|----------------------------------|------------------------------|
| NDA # 022523 | NDA Supplement #: S- | Efficacy Supplement Type SE- |
| Proprietary Name: Pancreaze Established/Proper Name: pancrelipase Dosage Form: Capsules Strengths: 4,200 USP Units Lipase/17,500 USP Units Amylase/10,000 USP Units Protease, 10,500 USP Units Lipase/45,750 USP Units Amylase/25,000 USP Units Protease, 16,800 USP Units Lipase/70,000 USP Units Amylase/40,000 USP Units Protease, 21,000 USP Units Lipase/61,000 USP Units Amylase/37,000 USP Units Protease | | |
| Applicant: Johnson & Johnson Research Development L.L.C. | | |
| Date of Receipt: June 23, 2009 | | |
| PDUFA Goal Date: April 23, 2010 | Action Goal Date (if different): | |
| Proposed Indication(s): Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions | | |

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

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



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

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

| | |
|---|---|
| Source of information* (e.g., published literature, name of referenced product) | Information provided (e.g., pharmacokinetic data, or specific sections of labeling) |
| Published literature | Nonclinical safety |

*each source of information should be listed on separate rows

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

- Clinical:

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

- Preclinical:

The applicant provides and relies on published literature.

RELIANCE ON PUBLISHED LITERATURE

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

YES NO

If "NO," proceed to question #5.

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

YES NO

If "NO," proceed to question #5.

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

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

YES NO

RELIANCE ON LISTED DRUG(S)

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

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

YES NO

If "NO," proceed to question #10.

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

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

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

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

N/A YES NO

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

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

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

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

YES NO

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

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

- b) Approved by the DESI process?

YES NO

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

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

- c) Described in a monograph?

YES NO

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

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO

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

If “**NO**”, proceed to question #9.

Name of drug(s) discontinued from marketing:

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

YES NO

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

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

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

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

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

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

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

YES NO

If “**NO**” to (a) proceed to question #11.

If “**YES**” to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES NO

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

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

Pharmaceutical equivalent(s):

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

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

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

YES NO

If **“NO”**, proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES NO

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

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

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

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

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

No patents listed *proceed to question #14*

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

YES NO

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

Listed drug/Patent number(s):

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

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

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

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

Patent number(s):

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

Patent number(s):

Expiry date(s):

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

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

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

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

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If "NO", please contact the applicant and request the documentation.

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

Date(s):

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

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

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

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

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

/s/

STACY R BARLEY
04/05/2010



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

Date: March 24, 2010

To: Donna Griebel, MD, Director
Division of Gastroenterology Products (DGP)

Through: Claudia Karwoski, PharmD, Director
Division of Risk Management (DRISK)

Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer, Acting Team Leader
Division of Risk Management

From: Steve L. Morin, RN, BSN
Patient Labeling Reviewer
Division of Risk Management (DRISK)

Jodi M. Duckhorn, MA
Senior Social Science Reviewer
Division of Risk Management (DRISK)

Subject: DRISK Review of Patient Labeling (Medication Guide),
Proposed Risk Evaluation and Mitigation Strategy (REMS)
Modification, and Proposed Methodology and Survey
Instruments for REMS Assessments

Drug Name(s): PANCREAZE (pancrelipase) Delayed Released Capsules
Application Type/Number: NDA 22-523
Applicant/sponsor: Ortho-McNeil-Janssen Pharmaceuticals, Inc

OSE RCM #: 2010-163

1 INTRODUCTION

This memorandum is in response to a request by the Division of Gastroenterology Products (DGP) for the Division of Risk Management (DRISK) to review the proposed Medication Guide (MG), proposed Risk Evaluation and Mitigation Strategy (REMS) and REMS supporting documents for PANCREAZE (pancrelipase) Delayed Released Capsules.

On June 23, 2009 Johnson and Johnson Pharmaceutical Research & development, LLC on behalf of McNeil Pediatrics, a Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc., submitted New Drug Application (NDA) 22-523 for PANCREAZE (pancrelipase) Delayed Released Capsules.

PANCREAZE (pancrelipase) Delayed Released Capsules has been marketed in the US since 1988 without a requirement to have an approved NDA. The company submitted an original NDA to fulfill the FDA requirement under 69 Federal Register [FR] 23410, 72 Federal Register [FR] 60860 that all pancreatic enzyme products are new drugs for which an NDA must be approved by April 28, 2010.

Additional reference is made to the FDA letter from October 01, 2009 which outlined the FDA's requirement that a REMS is necessary for PANCREAZE (pancrelipase) Delayed Released Capsules and other porcine-derived pancreatic enzyme products (PEPs) to ensure that the benefit of the drug outweigh the risk of fibrosing colonopathy associated with higher doses of PEPs, and the theoretical risk of transmission of viral disease to patients.

Please send these comments to the Applicant and request a response within two weeks of receipt. Let us know if you would like a meeting to discuss these comments before sending to the Applicant.

2 MATERIAL REVIEWED

- Draft PANCREAZE (pancrelipase) Delayed Released Capsules Prescribing Information (PI) submitted October 28, 2009 and revised by the review division throughout the review cycle.
- Draft PANCREAZE (pancrelipase) Delayed Released Capsules substantially complete PI dated March 3, 2010, provided to DRISK on March 8, 2010
- Draft PANCREAZE (pancrelipase) Delayed Released Capsules Medication Guide dated October 28, 2009 and revised by the review division throughout the review cycle
- PANCREAZE (pancrelipase) Delayed Released Capsules Risk Evaluation and Mitigation Strategy (REMS) Notification Letter dated September 14, 2009
- Proposed PANCREAZE (pancrelipase) Delayed Released Capsules Risk Evaluation and Mitigation Strategy (REMS) and REMS Supporting Document, submitted on October 19, 2009

3 RESULTS OF REVIEW

3.1 In our review of the Medication Guide, we have:

- Simplified wording and clarified concepts where possible
- Ensured that the MG is consistent with the PI
- Removed unnecessary or redundant information
- Ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- Ensured that the MG meets the criteria as specified in FDA's Guidance Useful Written Consumer Medication Information (published July 2006)

3.2 In our review of the proposed REMS and REMS Supporting Document, we have:

- Ensured it includes the elements outlined in the REMS Notification Letter
- Ensured it meets the statutory requirements under the Food and Drug Administration Amendments Act (FDAAA) of 2007.
- Reviewed the survey methodology for acceptability in assessing the goal of the REMS

4 CONCLUSIONS AND RECOMMENDATIONS

DRISK concurs with the elements of the REMS as proposed by the Applicant.

We have the following comments and recommendations for the Review Division and Applicant with regard to the MG, the proposed REMS and the REMS Assessment methodology.

Comments to Review Division:

Our annotated MG is appended to this memo (Appendix A Marked Copy, Appendix B Clean Copy). Any additional revisions to the PI should be reflected in the MG.

Comments to Applicant:

See the appended PANCREAZE (pancrelipase) Delayed Released Capsules REMS proposal (Appendix C of this memo) for track changes corresponding to comments in this review.

a. GOAL

Your goal is acceptable.

- b. We remind you of your responsibility to comply with 21 CFR 208.24, for ensuring that sufficient numbers of Medication Guides are provided with the product. We acknowledge you will provide an FPI with each bottle of PANCREAZE. However, please clarify each packaging configuration. For example:

- A minimum of 4 Medication Guides would be provided with a bottle of 100 for a product where the usual or average dose is 1 capsule/tablet daily, thus a monthly supply is 30 tablets.
 - A minimum of 1 Medication Guide would be provided with unit of use where it is expected that all tablets/capsules would be supplied to the patient.
- c. We acknowledge your inclusion of “an instruction alerting the pharmacist to provide a Medication Guide to each patient.” We recommend that you use one of the following two statements depending upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):
- “Dispense the enclosed Medication Guide to each patient.” Or
 - “Dispense the accompanying Medication Guide to each patient.”
- d. Your proposed timetable for submission of assessments (18 months, 3 years, and 7 years) is acceptable.
- e. We have some editorial comments in this section of the proposed REMS.

The submitted methodology lacks sufficient detail to complete a review.

Submit for review the detailed plan that will be used to evaluate patients’ understanding about the risks associated with and safe use of Pancreaze. This information **does not** need to be submitted for FDA review prior to approval of your REMS, however it should be submitted at least 90 days before the evaluation will be conducted. The submission should be coded “REMS Correspondence.” If the plan is to conduct the required assessment using a survey, the submission should include all methodology and instruments that will be used to evaluate the patients’ knowledge about the risks associated with and safe use of Pancreaze.

1. We encourage you to recruit respondents using a multi-modal approach. For example, patients could be recruited online, through physicians’ offices, through pharmacies, managed care providers, or through consumer panels.
 - Explain how often non-respondent follow-up or reminders will be completed.
 - Explain how an incentive or honorarium will be offered, and the intended amount.
 - Explain how recruitment sites will be selected.
 - Submit for review any recruitment advertisements.
2. Define the sample size and confidence intervals associated with that sample size.
3. Define the expected number of patients to be surveyed, and how the sample will be determined (selection criteria)
4. Explain the inclusion criteria; that is, who is an eligible respondent. For example, patient respondents might be:
 - Age 18 or older
 - Currently taking Pancreaze or have taken in past 3 months
 - Not currently participating in a clinical trial involving Pancreaze

- Not a healthcare provider

Submit any screener instruments, and describe if any quotas of sub-populations will be used.

5. Explain how surveys will be administered, and the intended frequency.

Offer respondents multiple options for completing the survey. This is especially important for inclusion of the lower literacy population. For example, surveys could be completed online or through email, in writing or by mail, over the phone, or in person.

Explain how surveyors will be trained.

6. Explain controls used to compensate for the limitations or bias associated with the methodology.
7. The patient sample should be demographically representative of the patients who use Pancreaze.

If possible and appropriate, sample should be diverse in terms of: age, race, ethnicity, sex, socio-economic status, education level, geography.

8. Submit for review the introductory text that will be used to inform respondents about the purpose of the survey.

Potential respondents should be told that their answers will not affect their ability to receive or take Pancreaze, and that their answers and personal information will be kept confidential and anonymous.

9. Respondents should not be eligible for more than one wave of the survey.

10. The assessment is to evaluate the effectiveness of the REMS in achieving the REMS goal by evaluating patients' knowledge of the serious risks associated with use of Pancreaze. The assessment is not to evaluate consumer comprehension of the Medication Guide.

Other than when the patient received the Medication Guide at the time the prescription was filled/dispensed, respondents should not be offered an opportunity to read or see the Medication Guide again prior to taking the survey.

11. Submit for review the survey instruments (questionnaires and/or moderator's guide), including any background information on testing survey questions and correlation to the messages in the Medication Guide.

12. The patient knowledge survey should include a section with questions asking about the specific risks or safety information conveyed in the Medication Guide to see if the patient not only understands the information, but knows what to do if they experience the event.

Most of the risk-specific questions should be derived from information located in the "What is the Most Important Information I should know about Pancreaze?" section of the Medication Guide. The questions should be about understanding the risk, the symptoms, and what to do if the event occurs.

The risk-specific questions should be non-biased, non-leading, multiple choice questions with the instruction to "select all that apply." Each question should have an "I don't know" answer option.

The order of the multiple choice responses should be randomized on each survey.

13. The order of the questions should be such that the risk-specific questions are asked first, followed by questions about receipt of the Medication Guide. Demographic questions should be collected last or as part of any screener questions.

Respondents should not have the opportunity or ability to go back to previous questions in the survey.

Explain if and when any education will be offered for incorrect responses.

14. Include questions about receipt of the Medication Guide in the patient survey as a way to fulfill the obligation to report on the distribution of the Medication Guide.
15. Just prior to the questions about receipt of the Medication Guide, include text that describes a Medication Guide. For example,

Now we are going to ask you some questions about the Medication Guide you may have received with Pancreaze. The Medication Guide is a paper handout that contains important information about the risks associated with use of Pancreaze and how to use Pancreaze safely. Medication Guides always include the title "Medication Guide".

16. Use the following (or similar) questions to assess receipt and use of the Medication Guide.
 - Who gave you the Medication Guide for Pancreaze? (Select all that apply)
 - My doctor or someone in my doctor's office
 - My pharmacist or someone at the pharmacy
 - Someone else - please explain: _____
 - I did not get a Medication Guide for Pancreaze
 - Did you read the Medication Guide?
 - All,
 - Most,
 - Some,
 - None
 - Did you understand what you read in the Medication Guide?
 - All,
 - Most,
 - Some,
 - None
 - Did someone offer to explain to you the information in the Medication Guide?
 - Yes, my doctor or someone in my doctor's office
 - Yes, my pharmacist or someone at the pharmacy
 - Yes, someone else – please explain:

 - No
 - Did you accept the offer? Yes or No
 - Did you understand the explanation that was given to you?

- All,
 - Most,
 - Some,
 - None
- Did or do you have any questions about the Medication Guide? Yes or No (If Yes, list your question(s) below) Note: This is an open text field that should be grouped/coded by the sponsor prior to submitting to FDA
17. Results should be analyzed on an item-by-item or variable-by-variable basis. The data may be presented using descriptive statistics, such as sample size, mean, standard deviation, median, minimum and maximum (for continuous variables), and frequency distributions (for categorical variables).
18. Data may be stratified by any relevant demographic variable, and also presented in aggregate. We encourage you to submit with your assessments all methodology and instruments that were used to evaluate the effectiveness of the REMS.
- f. Please let us know if you have any questions.

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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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/s/

STEVE L MORIN
03/24/2010

CLAUDIA B KARWOSKI
03/24/2010
concur

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE:

TO: Stacy Barley, Regulatory Project Manager
Ali Niak, Medical Officer
Division of Gastroenterology Products

FROM: Khairy Malek, Medical Officer
Good Clinical Practice Branch 2
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch 2
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA : 22-523

APPLICANT: Johnson & Johnson Pharmaceutical Research & Development. L.L.C

DRUG: Pancrease MT (pancrelipase)

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: Pancreatic Insufficiency and (b) (4)

CONSULTATION REQUEST DATE: August 10, 2009

DIVISION ACTION GOAL DATE: April 23, 2010

PDUFA DATE: April 23, 2010

I. BACKGROUND:

The new drug application was submitted to support the use of Pancrease MT (microtablet) Capsules in pancreatic insufficiency and (b) (4). These capsules contain microtablets in various dosage strengths including MT 4, MT 10, MT 16 & MT 20 and the active ingredient pancrelipase which is extracted from the pancreas of the hog.

One pivotal study was submitted in support of this application: Protocol: # and Title: PNCRLPCYS3001 “A Randomized Double-Blind (Withdrawal) Phase 3 Study to Evaluate the Efficacy and Tolerability of PANCREASE MT Capsules Compared With Placebo in the Treatment of Subjects with Cystic Fibrosis-Dependent Exocrine Pancreatic Insufficiency”.

The primary objective of the study was to evaluate the efficacy of Pancrease MT capsules 10 and 20, or a combination of both, on the quantitative change in fat absorption in adults and pediatric/adolescent CF subjects with clinical symptoms of exocrine pancreatic insufficiency (EPI). Overall safety was to be assessed as well.

The secondary objective was to evaluate the efficacy of Pancrease MT capsules on the quantitative change in protein absorption, as well as the evaluation of improvements in clinical signs of EPI (nausea, vomiting, bloating, diarrhea and abdominal pain).

The primary efficacy measure for this study was the change in Coefficient of fat absorption (COA-fat) from the 72-hour stool collection period at the end of the open-label phase to the 72-hour stool collection period at the end of the randomized, double-blind withdrawal phase.

II. RESULTS (by Site):

| Name of CI Location | Protocol #: and # of Subjects: | Inspection Date | Final Classification |
|--|--------------------------------|----------------------|----------------------|
| Richard Mathis, M.D, 2801 Atlantic Avenue Long Beach, CA 90806 | PNCRLPC YS3001 9 subjects | October 14- 23/09 | VAI |
| Arnold Platzker, M.D. 4650 Sunset Blvd Mail Stop 83 Los Angeles, CA 90027 | PNCRLPC YS3001 8 subjects | October 7- 8/09 | NAI |

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

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

1. Richard Mathis, M.D.- Site 001017

Miller Children's Hospital, 2801 Atlantic Ave, Long Beach, CA 90806

- a. What was inspected: At this site, 12 subjects were screened; 10 subjects were randomized and 9 subjects completed the study.

The field investigator reviewed the records of all 9 subjects in the study. All 9 subjects completed the study. There was no limitation to the inspection

- b. General observations/commentary: The field investigator reviewed the records of all 9 Subjects in the study.

Inspection revealed two violations: the CI did not maintain the nitrogen intake and COA-Protein source documents at the site. The field investigator was unable, as a result, to verify the secondary efficacy parameter. These records that were unavailable for review, are located at the sponsor's site, however. In speaking with the review division medical teamleader, the inability to verify the referenced secondary efficacy parameter is not considered critical to the evaluation of the application. The second violation was a protocol violation in that the first 3 subjects enrolled, were given a single blue dye capsules instead of two as required by the protocol

- c. Assessment of data integrity: Although violations were noted in the conduct of the study, these are unlikely to impact the validity of the data. The data generated at this site can be used in support of the NDA

2. Arnold Platzker, M.D.-Site 0010113

Children's Hospital Los Angeles, 4650 Sunset Blvd Mail Stop 83
Los Angeles, CA 90027

- a. What was inspected: The field investigator reviewed all 8 subjects in the study. All 8 subjects completed the study. There was no limitation of the inspection.

- b. General observations/commentary: The inspection revealed no violations of the federal regulations

- c. Assessment of data integrity: The data generated at this site can be used in support of the NDA.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical investigator sites were inspected in support of the application. No regulatory violations were noted at Dr. Platzker's site, and the regulatory violations noted at Dr. Mathis's site are unlikely to importantly impact primary efficacy data integrity as well as safety. The data generated at the above 2 sites can be used in support of the NDA indication.

{See appended electronic signature page}

Khairy Malek, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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

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/s/

KHAIRY W MALEK
03/15/2010

TEJASHRI S PUROHIT-SHETH
03/15/2010

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

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

Memorandum

Date: March 3, 2010

To: Stacy Barley, Regulatory Project Manager
Division of Gastroenterology Products (DGP)

From: Kathleen Klemm, Regulatory Review Officer
Shefali Doshi, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

CC: Lisa Hubbard, Professional Group Leader
Robert Dean, DTC Group Leader
Wayne Amchin, Regulatory Health Project Manager
DDMAC

Subject: NDA 22-523

DDMAC labeling comments for PANCREAZE[®] (pancrelipase) Capsules

In response to DGP's July 21, 2009, consult request, DDMAC has reviewed the draft labeling (PI, Carton and Container labeling and Medication Guide) for PANCREAZE[®] (pancrelipase) Capsules (NDA 22-523). DDMAC's comments on the PI and Medication Guide are based on the proposed draft marked-up labeling titled "draft-labeling-text-clean-october-2009-2.doc" that was modified in the e-room on March 1, 2010 at 1:57 pm.

DDMAC's comments on the PI and Medication are provided directly in the marked-up document attached (see below). Please also see below for DDMAC's comments on the Carton and Container labeling.

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

If you have any questions regarding the PI or Carton and Container labeling, please contact Kathleen Klemm at 301.796.3946 or Kathleen.Klemm@fda.hhs.gov. If you have any questions regarding the Medication Guide, please contact Shefali Doshi at 301.796.1780 or Shefali.Doshi@fda.hhs.gov.

Carton and Container Labeling

DDMAC has reviewed the following materials, accessed via the DGP e-room on March 1, 2010. These documents were last modified on July 21, 2009:

- pancrease-mt-10-carton-june-2009-as-ref-in-seq-0002.pdf
- pancrease-mt-16-carton-june-2009-as-ref-in-seq-0002.pdf
- pancrease-mt-20-carton-june-2009-as-ref-in-seq-0002.pdf
- pancrease-mt-4-carton-june-2009-as-ref-in-seq-0002.pdf
- pancrease-mt-10-label-june-2009-as-ref-in-seq-0002.pdf
- pancrease-mt-16-label-june-2009-as-ref-in-seq-0002.pdf
- pancrease-mt-20-label-june-2009-as-ref-in-seq-0002.pdf
- pancrease-mt-4-label-june-2009-as-ref-in-seq-0002.pdf

DDMAC has no comments on these proposed materials at this time.

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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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/s/

SHEFALI S DOSHI

03/03/2010

We hid formatting changes so our comments are easier to read.

CENTER FOR DRUG EVALUATION AND RESEARCH
MEDICAL NECESSITY DETERMINATION

INSTRUCTIONS

Please evaluate the medical need for this product by answering the questions below. Keep in mind that a medically necessary drug product is a product that is used to treat or prevent a serious disease or medical condition for which there is no other alternative drug that is judged by medical staff to be an adequate substitute. Patient “inconvenience” alone is an insufficient basis to classify a product as medical necessity.

NAME AND HFD NUMBER OF DIVISION: Division of Gastroenterology Products (HFD-180)

Name of person(s) making determination: Marjorie Dannis, M.D.

Date of Medical Necessity Request: January 12, 2010

PRODUCT(S): Pancreatic Enzymes which are currently unapproved (i.e., Axcan Pharma’s Ultrase and Viokase, and Digestive Care’s Pancrecarb as well as J&J’s Pancrease MT)

BACKGROUND:

After the 4/28/10 FR notice deadline, approximately 50% of the market will continue to be held by unapproved products (Ultrase and Viokase from Axcan as well as Pancrecarb from Digestive Care and Pancrease MT from J&J.)

From previous consultations on medical need, it is known that the pancreatic enzyme products in general are medically necessary; however, Compliance has asked if these specific unapproved products are medically necessary or if the approved products (Creon from Solvay and Zenpep from Eurand) can be substituted. If there are patients for which the unapproved products are medically necessary, possibly a treatment IND could be instituted with the company to continue availability for specific patients based on medical need.

1. Is the product used to treat a serious disease or medical condition?

[] No

[X] Yes – Explain

Pancreatic enzyme products (PEPs) are used to treat exocrine pancreatic insufficiency (EPI) due to a variety of causes. There are approximately 30,000 pediatric and adult patients with cystic fibrosis (CF) in the United States; the majority of these patients suffer from EPI. In addition, there are approximately 200,000 patients with EPI due to various forms of pancreatitis including chronic pancreatitis.

Patients affected with CF-related EPI and other patients with EPI have a clinically significant reduction of pancreatic function and are unable to fully digest fats, proteins, and carbohydrates. As a consequence, these patients tend to develop malabsorption of these nutrients, with resultant malnutrition and secondary complications such as impaired immune response, infections, bleeding tendencies, fat soluble vitamin deficiencies, and other signs and symptoms of malnutrition. Additionally, children with CF-related EPI have impaired growth and development. Thus, as a therapeutic class, PEPs are used to treat a serious condition.

2. What are the labeled indications for this product?

As stated in the Background section above, each of these products are currently marketed but are not approved. Based on the unapproved labels, the current indications for each product are listed below^{1,2,3,4}:

- A. “VIOKASE® (pancrelipase, USP) is indicated in the treatment of exocrine pancreatic insufficiency as associated with but not limited to cystic fibrosis, chronic pancreatitis, pancreatectomy, or obstruction of the pancreas ducts.”
- B. “ULTRASE® (pancrelipase) capsules are indicated for patients with partial or complete exocrine pancreatic insufficiency caused by:
 - Cystic fibrosis (CF)
 - Chronic pancreatitis due to alcohol use or other causes
 - Surgery (pancreatico-duodenectomy or Whipple's procedure, with or without Wirsung duct injection, total pancreatectomy)
 - Obstruction (pancreatic and biliary duct lithiasis, pancreatic and duodenal neoplasms, ductal stenosis)
 - Other pancreatic disease (hereditary, post traumatic and allograft pancreatitis, hemochromatosis, Shwachman's Syndrome, lipomatosis, hyperparathyroidism)
 - Poor mixing (Billroth II gastrectomy, other types of gastric bypass surgery, gastrinoma)”
- C. “PANCRECARB® (pancrelipase) Delayed-Release Capsules are indicated for patients with exocrine pancreatic insufficiency such as: cystic fibrosis, chronic pancreatitis due to alcohol use or other causes, post- pancreatectomy, and post gastrointestinal bypass surgery (e.g. Bilroth II gastroenterostomy)”

¹ http://www.axcan.com/pdf/viokase_info.pdf (accessed February 18, 2010)

² http://www.ultrase.com/pdf/ultrase_info.pdf (accessed February 18, 2010)

³ http://www.digestivecare.com/pdf/DCI_Pancrecarb_PI_08.pdf (accessed February 18, 2010)

⁴ http://www.mcneilpediatrics.net/mcneilpediatrics/shared/pi/pancrease_mt.pdf (accessed February 18, 2010)

D. "PANCREASE MT is indicated for the treatment of steatorrhea secondary to pancreatic insufficiency such as in cystic fibrosis or chronic alcoholic pancreatitis."

3. Are there important "off label" uses such as those for a serious medical condition?

- No
 Yes

4. Are there generic forms of this product?

- No
 Yes — Are there any special benefits/risks associated with the generic product(s)?

5. Are there alternative products available?

- No
 Yes – Please explain the risk(s) and benefit(s) of this alternative product.

PEPs are comprised of lipase, amylase and protease, which are the active ingredients (enzymes) which aid in the digestion of fats, proteins and carbohydrates. Generally, PEPs come in two types of preparations: enteric-coated and non-enteric coated. Historically, the non-enteric coated preparations were marketed initially; however, because the enzymes (lipase, amylase and protease) can be degraded by the acidic gastric environment, enteric-coated preparations of pancreatic enzymes were developed.

Currently, there are a large variety of PEPs available on the market. These include the recently approved products (Creon and Zenpep) as well as the unapproved products (Ultrase, Viokase, Pancrecarb and Pancrease MT). Creon, Zenpep, Ultrase, Pancrecarb and Pancrease MT are all enteric-coated preparations. Viokase is a non-enteric coated preparation.

Theoretically, patients taking one brand of enteric-coated PEP should easily be switched to another enteric-coated preparation, although some titration of doses may be necessary. Subsequently, patients currently taking one of the unapproved enteric-coated formulations (i.e., Ultrase, Pancrecarb or Pancrease MT) could readily be switched to one of the approved enteric-coated formulations (i.e., Creon or Zenpep). It is possible that many patients have already switched to one of the two approved products.

Patients currently taking the unapproved non-enteric-coated formulation (i.e., Viokase) may also be switched to one of the approved enteric-coated formulations. Again, some dose titration may be necessary to achieve full effectiveness. There is some thinking that the non-enteric coated enzyme preparations may be uniquely beneficial to patients with chronic pancreatitis and for control of the pain associated with this condition.⁵ Other experts in the field argue that the studies performed to verify that non-enteric coated preparations are more effective in alleviating pain secondary to chronic pancreatitis have shown equivocal results.⁶

⁵ Toskes, PP. Update on diagnosis and management of chronic pancreatitis. *Curr Gastroenterol Rep.* 1999 Apr;1(2):145-53.

⁶ Fasanella KE, Davis B, Lyons J, Chen Z, Lee KK, Slivka A, Whitcomb DC. Pain in chronic pancreatitis and cancer. *Gastroenterol Clin North Am.* 2007 Jun;36(2):335-64, ix.

Although PEPs may be helpful for treatment of pain secondary to chronic pancreatitis, there are alternative therapies available for pain control. Pain secondary to chronic pancreatitis may be successfully treated with nonsteroidal anti-inflammatory medications or acetaminophen, narcotics, octreotide (a synthetic analog of somatostatin that is believed to inhibit pancreatic secretion and lower CCK levels), or more invasive surgical procedures.⁷

It is possible that there exists a subset of patients whose pain has historically responded better to treatment with non-enteric coated enzyme preparations as compared to enteric-coated preparations. However, it is likely that these patients will respond to one of the two newly approved enteric-coated preparations.

Each of the approved products has been reviewed under NDA and has been deemed acceptable from a clinical safety and efficacy standpoint as well as from a CMC standpoint. The currently marketed unapproved products have never undergone this process, and thus could potentially be less efficacious and less safe than the approved products. Accordingly, a switch from one of the unapproved products to one of the approved products (Creon or Zenpep) would offer patients potentially greater benefit and less risk.

- 6. From the above assessment, is this product Medically Necessary?** (Please note that this question refers only to the overall Medical Necessity of the product(s), not whether the specific (manufacturer's) product in question is appropriate for continued administration to patients. If the product is determined to be Medically Necessary, an assessment will then be made as to whether the product in question may be used (for instance with additional testing if necessary) to alleviate shortage situations. If it is not appropriate to administer such material to patients then alternative approaches will be examined. When necessary, a separate Health Hazard Evaluation [HHE] will be requested to address newly identified defects, impurities and/or risks associated with this drug.

No

Yes (Please state if this is only for specific indications)

7. Additional comments:

Ultrase, Viokase, Pancrecarb and Pancrease MT are not medically necessary drug products since Creon and Zenpep are acceptable substitutes. There may be a subset of patients who are stable on Viokase therapy for pain control that experience more difficulty switching to an enteric-coated preparation. However, Viokase (in addition to the other PEPs) is not indicated for the treatment of pain associated with chronic pancreatitis. Additionally, many alternative therapies exist for pain control.

⁷ Warsaw AL, Banks PA, Fernandez-Del Castillo C. AGA technical review: treatment of pain in chronic pancreatitis. *Gastroenterology* 1998;115:765-76.

8. Signature of person performing this medical necessity determination.

{See appended electronic signature page}

Medical Officer Date

{See appended electronic signature page}

Medical Officer, Team Leader Date

{See appended electronic signature page}

Division Director Date

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

(b) (4)

NDA-22523

GI-1

JOHNSON &
JOHNSON
PHARMACEUTICA
L RESEARCH &
DEVELOPMENT
LLC

Pancrelipase Microtablets

(b) (4)

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/s/

MARJORIE F DANNIS
02/19/2010

ANIL K RAJPAL
02/19/2010

DONNA J GRIEBEL
02/22/2010



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

Date: February 17, 2010

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

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

From: Anne Crandall, Pharm.D., Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name(s): Pancreaze (Pancrelipase) Capsule,
4,200 USP Units Lipase/17,500 USP Units Amylase/10,000 USP
Units Protease,
10,500 USP Units Lipase/43,750 USP Units Amylase/25,000 Units
USP Protease,
16,800 USP Units Lipase/70,000 USP Units Amylase/40,000 USP
Units Protease,
21,000 USP Units Lipase/61,000 USP Units Amylase/37,000 USP
Units Protease

Application Type/Number: NDA 022523

Applicant: Johnson & Johnson Pharmaceutical Research and Development

OSE RCM #: 2009-1215

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| 3.1 | FDA Adverse Event Reporting System (AERS) Database..... | 1 |
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1 INTRODUCTION

This review was written in response to a request from the Division of Gastroenterology Products for assessment of the container labels, carton and insert labeling for Pancreaze (Pancrelipase Capsules) submitted November 9, 2009. This submission also included the request to review the proposed proprietary, Pancreaze, which was evaluated under a separate cover.

2 METHODS AND MATERIALS

2.1 FDA ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE

Pancreaze tablets are currently marketed therefore, DMEPA conducted a search of the FDA Adverse Event Reporting System (AERS) database on January 5, 2009, to identify medication errors involving Pancreaze.

The MedDRA High Level Group Term (HLGT) “Medication Errors”, the High Level Term (HLT) “Product Label Issues” and the Preferred Term (PT) “Product Quality Issues” were used as search criteria for Reactions. The search criteria used for Products was verbatim substance search “Pancreaze%”. No date limitations were set.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the labels or labeling of the product, the case was considered pertinent to this review. Those reports that did not describe a medication error or did not describe an error applicable to this review (e.g. errors related to accidental exposures, intentional overdoses, etc.) were excluded from further analysis.

2.2 LABEL AND LABELING

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis (FMEA)¹ in our evaluation of the labels and labeling submitted as part of the November 9, 2009 submissions (see Appendix A).

3 RESULTS

3.1 FDA ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE

The AERS search conducted on January 5, 2009, yielded three cases. Two cases were excluded from further evaluation because the cases involved product complaints associated with labeled adverse events (excessive bloating, gas and weight loss) due to Pancreaze therapy. There was no indication that an error had occurred with regards to dosing.

The third case reported an error due to name confusion between Pancreaze and Pacerone. A pharmacy technician filled the prescription on refill with Pacerone and the pharmacist checked the order. The medication error reached the patient, however it is difficult, based on the report, to determine whether the patient took the medicine as it seems the error may have been discovered when dispensed to the patient.

An additional AERS Interaction search was run which focused on the products Pancreaze and Pacerone. The search used the verbatim “Pancreaze%” and “Paceron%” and the tradename “Pacerone”. No additional cases were found during this search. The potential name confusion between Pacerone and Pancreaze was evaluated during the proprietary name review, OSE review #2009-2253.

¹ Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

3.2 LABEL AND LABELING

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

4 CONCLUSIONS AND RECOMMENDATIONS

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

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

4.1 COMMENTS TO THE APPLICANT

A. Container Labels (Applies to all strengths)

1. In accordance with 21 CFR 201.10 (g)(2), ensure that the established name is printed in letters that are commensurate with the proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.
2. Revise your container labels so that the three active ingredients are boxed as follows:

| | |
|-----------------------|----------------|
| Each tablet contains: | |
| Lipase | XXXX USP Units |
| Amylase | XXXX USP Units |
| Protease | XXXX USP Units |

Boxes will represent the product strength on the principle display panel. The boxes should be prominently displayed, following the proprietary and established names, and should utilize a unique color to represent each of the four strengths of Pancreaze as recognized by the Lipase units.

3. Reconfigure the statement “Dose by Lipase units” on the principal display panel beside the strength designation box to read left to right, rather than downward. Additionally, the statement should be relocated so that it follows the strength designation box.
4. In accordance with 21 CFR 208.24 (2)(d) ensure that the container labels contain the statement, “Attention Pharmacist: Dispense the accompanying Medication Guide to each patient” on the principal display panel. This statement should not intervene with other pertinent information, e.g. strength, established name, etc.
5. Relocate the net quantity statement to ensure that there is no intervening matter between the established name and the strength statement.
6. As currently presented, the ‘McNeil Pediatrics’ statement on the principal display panel

appears as prominent as the proprietary name and established name. Decrease the prominence of the of the 'McNeil Pediatrics' statement to ensure that the proprietary name and established name are the most prominent information on the principal display panel.

B. Carton labeling (Applies to all strengths)

See comments A1 through A3 and apply to carton labeling.

C. Container Label and Carton Labeling (10,500 USP Units Lipase and 16,800 USP Units Lipase)

Consider using a different color either for the 10,500 USP Units/43,750 USP Units/25,000 USP Units or the 16,800 USP Units/70,000 USP Units/40,000 USP Units as the hues of pink and red resemble one another and should be better differentiated to avoid errors in product selection.

4 Page(s) has (have) been Withheld in Full immediately following this page as B4 (CCI/TS)

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

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

/s/

ANNE CRANDALL
02/17/2010

MELINA N GRIFFIS
02/17/2010

DENISE P TOYER
02/18/2010

DENISE P TOYER on behalf of CAROL A HOLQUIST
02/18/2010

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Gastroenterology Products

Application Number: NDA 022523

Name of Drug: TRADENAME (pancrelipase) Capsules

Applicant: Johnson & Johnson Pharmaceutical Research Development L.L.C.

Material Reviewed:

Submission Date(s): June 23, 2009

Receipt Date(s): June 23, 2009

Submission Date of Structure Product Labeling (SPL): June 23, 2009

Type of Labeling Reviewed: WORD & SPL

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following issues/deficiencies have been identified in the sponsors proposed labeling.

- I. Highlights of Prescribing Information
 - a. Each summarized statement should reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
 - b. References in Highlights should use a numerical identifier in parentheses [e.g., (1.1)] corresponding to the location of information in the FPI and should follow the summarized labeling information.
 - c. The “R” symbol (e.g., “®”) should not be used after the drug name in Highlights or the Table of Contents. You may use this symbol once in the FPI.

- d. A product is a member of an established pharmacologic class. The following statement must appear under the Indications and Usage heading in the Highlights [21 CFR 201.57(a)(6)]:

“Tradename is a (name of class) indicated for (indication(s)).”

- e. Tabular format should be used to enhance accessibility of the Dosage and Administration information when there are different dosing regimens for different indications.
- f. A revision date for a new NDA should be left blank at the time of submission and will be edited to the month/year of application approval [21 CFR 201.57(a)(15)].

II. Full Prescribing Information (FPI)

- a. The subheading for subsection 8.3 is currently “Lactation” and must be “**Nursing Mothers**” [21 CFR 201.56 (d)(1)].
- b. Identifying numbers must be presented in bold print and must precede the heading or subheading by at least two square em’s (e.g., two squares of the size of the letter “m” in 8 point type) [21 CFR 201.57 (d)(7)].

Recommendations

The above deficiencies should be conveyed to the sponsor and the sponsor should re-submit labeling by November 19, 2009. This updated version of labeling will be used for further labeling discussions.

Stacy Barley, RN, MSN, MHA
Regulatory Health Project Manager

Supervisory Comment/Concurrence:

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff

Drafted: SB/ September 14, 2009

Revised/Initialed: September 18, 2009

Finalized: September 18, 2009

Filename: CSO Labeling Review Template (updated 1-16-07).doc

CSO LABELING REVIEW OF PLR FORMAT

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

/s/

STACY R BARLEY
09/18/2009

BRIAN K STRONGIN
09/18/2009

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

| Application Information | | |
|--|--|----------------------------------|
| NDA # 022523 BLA# N/A | NDA Supplement #:S- N/A BLA STN # N/A | Efficacy Supplement Type SE- N/A |
| Proprietary Name: Established/Proper Name: pancrelipase Dosage Form: capsule Strengths: 4,200, 10,500, 16,800 and 21,000 units of lipase | | |
| Applicant: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. Agent for Applicant (if applicable): N/A | | |
| Date of Application: June 23, 2009 Date of Receipt: June 23, 2009 Date clock started after UN: | | |
| PDUFA Goal Date: April 23, 2010 | Action Goal Date (if different): | |
| Filing Date: August 22, 2009 | Date of Filing Meeting: July 30, 2009 | |
| Chemical Classification: (1,2,3 etc.) (original NDAs only) 7 | | |
| Proposed Indication(s): Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions | | |
| Type of Original NDA: AND (if applicable) | <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) | |
| Type of NDA Supplement: | <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) | |
| Refer to Appendix A for further information. | | |
| Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i> | <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical disease Priority review voucher submitted | |
| Resubmission after withdrawal? <input type="checkbox"/> Resubmission after refuse to file? <input type="checkbox"/> | | |
| Part 3 Combination Product? <input type="checkbox"/> | <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device | |
| <input checked="" type="checkbox"/> Fast Track <input checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other: | <input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR | |

| | |
|---|--|
| 601.42) | |
| Collaborative Review Division (if OTC product): | |
| List referenced IND Number(s): IND 74893 | |
| PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i> | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i> | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i> | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| Application Integrity Policy | |
| Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ora/compliance_ref/aiplist.html If yes, explain: If yes, has OC/DMPQ been notified of the submission? Comments: | <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO |
| User Fees | |
| Form 3397 (User Fee Cover Sheet) submitted | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| User Fee Status Comments: | <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required |
| <i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i> | |

| Exclusivity | |
|---|---|
| <p>Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</i></p> <p>If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p>Comments:</p> | <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDA/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p>Comments:</p> | <input checked="" type="checkbox"/> YES # years requested: 3 <input type="checkbox"/> NO |
| <p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDA only</i>):</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p> | <input checked="" type="checkbox"/> Not applicable <input type="checkbox"/> YES <input type="checkbox"/> NO |
| 505(b)(2) (NDA/NDA Efficacy Supplements only) | |
| <p>1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p> <p>2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).</p> <p>3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made</p> | <input type="checkbox"/> Not applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO |

available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?

Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).

| <p>4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</p> | | <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO | | | | | | | | | | | | | | | | |
|---|-----------|---|------------------------|-----------|------------------|------------------------|--|--|--|--|--|--|--|--|--|--|--|--|
| <p>If yes, please list below:</p> <table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table> | | | Application No. | Drug Name | Exclusivity Code | Exclusivity Expiration | | | | | | | | | | | | |
| Application No. | Drug Name | Exclusivity Code | Exclusivity Expiration | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | |
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| | | | | | | | | | | | | | | | | | | |
| <p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p> | | | | | | | | | | | | | | | | | | |
| <p>Format and Content</p> | | | | | | | | | | | | | | | | | | |
| <p>Do not check mixed submission if the only electronic component is the content of labeling (COL).</p> <p>Comments:</p> | | <input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD) | | | | | | | | | | | | | | | | |
| <p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p> | | | | | | | | | | | | | | | | | | |
| <p>If electronic submission: <u>paper</u> forms and certifications signed (non-CTD) or <u>electronic</u> forms and certifications signed (scanned or digital signature)(CTD)?</p> <p><i>Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p> <p>Comments:</p> | | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO | | | | | | | | | | | | | | | | |
| <p>If electronic submission, does it follow the eCTD guidance? (http://www.fda.gov/cder/guidance/7087rev.pdf)</p> <p>If not, explain (e.g., waiver granted):</p> | | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO | | | | | | | | | | | | | | | | |

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

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

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

| OTC Labeling | |
|---|---|
| <p>Check all types of labeling submitted.</p> <p>Comments:</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify) |
| <p>Is electronic content of labeling submitted?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p> | <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <p>Are annotated specifications submitted for all stock keeping units (SKUs)?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p> | <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <p>If representative labeling is submitted, are all represented SKUs defined?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p> | <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <p>Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?</p> <p>Comments:</p> | <input type="checkbox"/> YES <input type="checkbox"/> NO |
| Meeting Minutes/SPA Agreements | |
| <p>End-of Phase 2 meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments:</p> | <input checked="" type="checkbox"/> YES Date(s): January 16, 2008 <input type="checkbox"/> NO |
| <p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments:</p> | <input checked="" type="checkbox"/> YES Date(s): December 3, 2008 <input type="checkbox"/> NO |
| <p>Any Special Protocol Assessment (SPA) agreements?</p> <p><i>If yes, distribute letter and/or relevant minutes before filing meeting.</i></p> <p>Comments:</p> | <input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO |

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 30, 2009

NDA/BLA #: 022523

PROPRIETARY/ESTABLISHED NAMES: Pancrease MT (pancrelipase microtablets)

APPLICANT: Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

BACKGROUND: Pancrease MT (pancrelipase microtablets) was originally submitted under IND 74,893 in June 2006 for the treatment of exocrine pancreatic insufficiency by Johnson and Johnson Pharmaceutical Research and Development L.L.C.. Pancrease MT was then submitted under NDA 22,523 in June 2009. No other Division is involved with this NDA.

Regarding worldwide marketing history, according to Johnson & Johnson, Pancrease MT is available in various countries throughout the world. J & J also stated Pancrease MT 4, 10, and 16 have been marketed in the United States since June 1988 for the treatment of steatorrhea secondary to pancreatic insufficiency in certain disorders such as cystic fibrosis. Pancrease MT 25 and 32 were introduced in the United States in December 1991 and July 1993. Intestinal strictures and colonic fibrosis associated with the use of high-strength pancreatic enzyme products were noted in January 1994. The Pancrease MT products containing >20,000 units of lipase activity per capsule was voluntarily withdrawn within the United States by the pharmaceutical company.

REVIEW TEAM:

| Discipline/Organization | Names | | Present at filing meeting? (Y or N) |
|---|-----------|--------------------------------|-------------------------------------|
| Regulatory Project Management | RPM: | Stacy Barley | Y |
| | CPMS/TL: | Brian Strongin Cristi Stark | Y |
| Cross-Discipline Team Leader (CDTL) | | | |
| Clinical | Reviewer: | Ali Niak | Y |
| | TL: | Anil Rajpal | Y |
| Social Scientist Review (<i>for OTC products</i>) | Reviewer: | | |
| | TL: | | |
| Labeling Review (<i>for OTC products</i>) | Reviewer: | | |

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|---|-----------|--|--|
| | | | |
| | TL: | | |
| OSE | Reviewer: | | |
| | TL: | | |
| Clinical Microbiology (<i>for antimicrobial products</i>) | Reviewer: | | |
| | TL: | | |

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|--|---|--------------------|---|
| Clinical Pharmacology | Reviewer: | Lanyan (Lucy) Fang | Y |
| | TL: | Jang-Ik Lee | Y |
| Biostatistics | Reviewer: | Shahla Farr | Y |
| | TL: | Michael Welch | Y |
| Nonclinical (Pharmacology/Toxicology) | Reviewer: | Ke Zhang | Y |
| | TL: | David Joseph | Y |
| Statistics, carcinogenicity | Reviewer: | | |
| | TL: | | |
| Product Quality (CMC) | Reviewer: | Howard Anderson | Y |
| | TL: | Emanuela Lacana | Y |
| Facility (<i>for BLAs/BLA supplements</i>) | Reviewer: | | |
| | TL: | | |
| Microbiology, sterility (<i>for NDAs/NDA efficacy supplements</i>) | Reviewer: | Bryan Riley | N |
| | TL: | James McVay | N |
| Bioresearch Monitoring (DSI) | Reviewer: | | |
| | TL: | | |
| Other reviewers: DMEPA | Safety Evaluator: Anne Crandall, Irene Chan, Melina Griffis | | Y |

OTHER ATTENDEES: Donna Griebel, Maria Walsh, Elizabeth Ford

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

| | |
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| <p>Electronic Submission comments</p> <p>List comments:</p> | <input type="checkbox"/> Not Applicable |
| <p>CLINICAL</p> <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p> | <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> | <input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: |
| <ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <p>CLINICAL PHARMACOLOGY</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE |

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| Comments: | <input type="checkbox"/> Review issues for 74-day letter |
| <ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? | <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO |
| BIOSTATISTICS Comments: Information request to be issued for stating the original protocol and SAP were not included in the submission. | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments: Waiting for information request issued on July 22, 2009. | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| PRODUCT QUALITY (CMC) Comments: | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <ul style="list-style-type: none"> Establishment(s) ready for inspection? <ul style="list-style-type: none"> Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <ul style="list-style-type: none"> Sterile product? | <input type="checkbox"/> YES |

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|---|--|
| <p>If yes, was Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</p> | <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <p>FACILITY (BLAs only)</p> <p>Comments:</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Julie Beitz

GRMP Timeline Milestones:

| | |
|--|---|
| Letter date of application | 6/23/09 |
| Receipt date of application | 6/23/09 |
| Filing Meeting | 7/30/09 |
| Team Meeting #1 | 8/26/09 |
| Team Meeting #2 | 9/17/09 |
| Team Meeting #3 | 10/15/09 |
| Additional team meeting | (TBD) |
| Mid-Cycle Review Meeting | 11/19/09 |
| Clinical meeting | (TBD) |
| PERC | Mid Jan (TBD) |
| Team Meeting #4 | (TBD) |
| Pre-approval safety conference | Early April (TBD) |
| Draft reviews due to team leaders | 2/27/10 |
| Final reviews signed off in DFS | 3/15/10 |
| Labeling/PMC team meetings (7) | 1/21/10, 1/28/10, 2/3/10, 2/11/10, 2/24/10, 3/3/10, 3/11/10 |
| CDTL Review due | 3/22/10 |
| Action pkg. to Division Director | 3/22/10 |
| Action pkg. to Office Director | 4/12/10 |
| PDUFA Goal Date | 4/23/10 |

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

| | |
|-------------------------------------|--|
| <input type="checkbox"/> | The application is unsuitable for filing. Explain why: |
| <input checked="" type="checkbox"/> | The application, on its face, appears to be suitable for filing. <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review |
| ACTIONS ITEMS | |
| <input checked="" type="checkbox"/> | Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system. |
| <input type="checkbox"/> | If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER. |
| <input type="checkbox"/> | If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review. |
| <input type="checkbox"/> | If BLA or priority review NDA, send 60-day letter. |
| <input type="checkbox"/> | Send review issues/no review issues by day 74 |
| <input type="checkbox"/> | Other |

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

STACY R BARLEY
08/20/2009

BRIAN K STRONGIN
08/20/2009