

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022523Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 022523

SUPPL #

HFD # 180

Trade Name Pancreaze

Generic Name pancrelipase

Applicant Name Johnson & Johnson Pharmaceutical Research & Development, LLC

Approval Date, If Known April 23, 2010

### **PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

### 1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO



Investigation #1  
!  
! YES  NO   
! Explain: ! Explain:

Investigation #2  
!  
! YES  NO   
! Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES  NO

If yes, explain:

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Name of person completing form: Stacy Barley, R.N., M.S.N., M.H.A.  
Title: Senior Regulatory Health Project Manager  
Date: April 5, 2010

Name of Office/Division Director signing form: Donna Griebel, M.D.  
Title: Director, Division of Gastroenterology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

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/s/

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STACY R BARLEY  
04/05/2010

DONNA J GRIEBEL  
04/08/2010

**DEBARMENT CERTIFICATION**

**PANCREASE® MT**

Johnson & Johnson Pharmaceutical Research & Development, L.L.C. certifies that we 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.



Donna Panasewicz  
Sr. Director  
Global Regulatory Affairs, Mature Products

  
Date

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 22523 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Pancreaze Established/Proper Name: pancrelipase Dosage Form: Delayed-Release Capsule		Applicant: Ortho-McNeil-Janssen Pharmaceuticals, Inc. Agent for Applicant (if applicable): Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
RPM: Stacy Barley, R.N., M.S.N., M.H.A.		Division: Division of Gastroenterology Products
<p><b>NDA:</b> NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A 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). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #s) and drug name(s):</p> <p>Reliance on literature</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input checked="" type="checkbox"/> If no listed drug, check box and explain:</p> <p><b>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to <a href="#">CDER OND IO</a> for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input type="checkbox"/> No changes    <input type="checkbox"/> Updated    Date of check: 4/12/10</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p>
❖ Actions		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>April 23, 2010</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input checked="" type="checkbox"/> None
<p>❖ If accelerated approval, were promotional materials received? Note: For accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a>). If not submitted, explain _____</p>		<input type="checkbox"/> Received

<sup>1</sup> The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics <sup>2</sup>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority          Chemical classification (new NDAs only): 7</p> <p><input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch  <input checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch  <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H <span style="margin-left: 200px;">BLAs: Subpart E</span>  <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <span style="margin-left: 100px;"><input type="checkbox"/> Accelerated approval (21 CFR 601.41)</span>  <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <span style="margin-left: 100px;"><input type="checkbox"/> Restricted distribution (21 CFR 601.42)</span>          Subpart I <span style="margin-left: 200px;">Subpart H</span>  <input type="checkbox"/> Approval based on animal studies <span style="margin-left: 100px;"><input type="checkbox"/> Approval based on animal studies</span></p> <p><input type="checkbox"/> Submitted in response to a PMR  <input type="checkbox"/> Submitted in response to a PMC  <input type="checkbox"/> Submitted in response to a Pediatric Written Request</p> <p>Comments:</p>	
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM ( <i>approvals only</i> )	<input type="checkbox"/> Yes, date N/A
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<sup>2</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire N/A no reference listed drug
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes       No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

*If "Yes," skip to question (4) below. If "No," continue with question (2).*

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes       No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

*If "No," continue with question (3).*

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes       No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

*If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes       No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).*

*If "No," continue with question (5).*

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
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**CONTENTS OF ACTION PACKAGE**

❖ Copy of this Action Package Checklist <sup>3</sup>	4/12/10
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) 4/12/10
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	4/12/10
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	6/23/09
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	8/27/09 Zenpep

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.  
Version: 12/4/09

❖ Medication Guide/Patient Package Insert/Instructions for Use ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	4/12/10
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	6/23/09
<ul style="list-style-type: none"> <li>Example of class labeling, if applicable</li> </ul>	
❖ Labels ( <b>full color</b> carton and immediate-container labels) ( <i>write submission/communication date on upper right of first page of each submission</i> )	
<ul style="list-style-type: none"> <li>Most-recent draft labeling</li> </ul>	4/6/2010
❖ Proprietary Name <ul style="list-style-type: none"> <li>Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>Review(s) (<i>indicate date(s)</i>)</li> </ul>	2/3/10 ("Pancreaze" acceptable); 8/13/09 ("Pancreaze MT" withdrawn) 1/25/10 Review complete
❖ Labeling reviews ( <i>indicate dates of reviews and meetings</i> )	<input checked="" type="checkbox"/> RPM 9/18/09 <input checked="" type="checkbox"/> DMEPA 2/18/10 <input checked="" type="checkbox"/> DRISK 3/24/10 <input checked="" type="checkbox"/> DDMAC 3/3/10 <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews OBP RPM: 4/12/10
<b>Administrative / Regulatory Documents</b>	
❖ Administrative Reviews ( <i>e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting</i> ) ( <i>indicate date of each review</i> )	8/20/09
❖ 505(b)(2) Assessment ( <i>indicate date</i> )	<input type="checkbox"/> Not a (b)(2) 4/5/10
❖ NDAs only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>Applicant in on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>This application is on the AIP <ul style="list-style-type: none"> <li>If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>Date reviewed by PeRC <u>3/31/10</u> If PeRC review not necessary, explain: _____</li> <li>Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent ( <i>include certification</i> )	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications ( <i>letters (except action letters), emails, faxes, telecons</i> )	4/12/10, 4/9/10, 4/8/10, 4/8/10, 4/2/10, 4/2/10, 4/2/10, 3/26/10, 3/25/10, 3/25/10, 3/22/10, 3/17/10,

<sup>4</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.  
Version: 12/4/09

	3/2/10, 2/24/10, 1/26/10, 1/22/10, 1/8/10, 12/23/09, 12/19/09, 12/10/10, 9/23/09, 9/1/09, 8/11/09, 7/22/09, 7/7/09
❖ Internal memoranda, telecons, etc.	8/17/09
❖ Minutes of Meetings	
• Regulatory Briefing ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg 12/3/08
• EOP2 meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg 1/16/08
• Other milestone meetings (e.g., EOP2a, CMC pilots) ( <i>indicate dates of mtgs</i> )	8/6/09
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available ( <i>do not include transcript</i> )	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4/12/10
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4/12/10
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4/12/10
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input type="checkbox"/> None 4/12/10 ten PMR/PMCs
<b>Clinical Information<sup>5</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	See CDTL review
• Clinical review(s) ( <i>indicate date for each review</i> )	draft, 8/18/09
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	See clinical review, 4/12/10 page 9
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management	
• REMS Documents and Supporting Statement ( <i>indicate date(s) of submission(s)</i> )	REMS 4/12/10, Supporting documents 10/19/09
• REMS Memo(s) and letter(s) ( <i>indicate date(s)</i> )	9/24/09
• Risk management review(s) and recommendations (including those by OSE and CSS) ( <i>indicate date of each review and indicate location/date if incorporated into another review</i> )	<input type="checkbox"/> None see DRISK review 3/24/10
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input type="checkbox"/> None requested Review (3/17/10); Letters 3/17/10, 3/15/10,

<sup>5</sup> Filing reviews should be filed with the discipline reviews.  
Version: 12/4/09

	3/15/10
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None 3/1/10 concurrence with stat review
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 3/1/10, 8/7/09
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None signed clinpharm review 3/15/10
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 3/15/10, 8/4/09
❖ DSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of DSI letters</i> )	<input checked="" type="checkbox"/> None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4/8/10
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4/8/10
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4/2/10
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary ( <i>include copies of DSI letters</i> )	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4/12/10 excutive summary, 4/12/10 review
❖ Microbiology Reviews	<input type="checkbox"/> Not needed 11/23/09, 7/20/09
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) ( <i>indicate date of each review</i> )	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) ( <i>indicate date of each review</i> )	N/A
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer ( <i>indicate date of each review</i> )	<input type="checkbox"/> None 3/10/10 ONDQA review of dissolution

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	Categorical exclusion granted per CMC review 4/12/10, page 4
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	N/A
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	N/A
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) ( <i>date completed must be within 2 years of action date</i> )	Date completed: 3/23/10 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<input type="checkbox"/> BLAs: TB-EER ( <i>date of most recent TB-EER must be within 30 days of action date</i> )	Date completed: N/A <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation ( <i>check box only, do not include documents</i> )	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed

## Appendix to Action Package Checklist

An NDA or NDA supplemental 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) **Or** 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.
- (3) **Or** 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) **And** 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.
- (3) **And** 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) **Or** 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.
- (3) **Or** 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 ODE's ADRA.

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

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/s/

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STACY R BARLEY  
04/13/2010

**From:** [Barley, Stacy](#)  
**To:** ["Scott, Ilona \[PRDUS\]"](#);  
**Subject:** RE: NDA 22523 Panreaze: REMS/REMS Supporting Document  
**Date:** Monday, April 12, 2010 11:38:35 AM

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Hello Ilona,

As discussed previously, Johnson and Johnson Pharmaceutical Research & Development, L.L.C. was originally listed as the "name of applicant" on the FDA form 356h when the June 23, 2009 submission arrived for NDA 22523. We noticed the sponsor name changed on the March 29, 2010 submission. The name is now listed as McNeil Pediatrics (a Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.). We request that J&J and Ortho-McNeil submit two formal letters to the NDA to document this transfer of ownership.

Additionally, We have the following requests:

- Edit your REMS to reflect the name of the sponsor holder as applicable. Additionally, section II.REMS ELEMENTS should have a subsection B. Timetable for Submission of Assessment (see attachment)

## **B. Timetable For Submission Of Assessments**

*Insert Exact "Name of Applicant" as identified on 356h* will submit REMS assessments to FDA 18 months, 3 years, and 7 years from the date of initial approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment.

*Insert Exact "name of Applicant" as identified on 356h* will submit each assessment so it will be received by the FDA on or before the due date.

- Please make revisions to PMC #5 to state the following:

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.

### **Final Report Submission by March 31, 2013**

- Edit Section 8.4 (third paragraph) of the label to say the following:

Study 2 was a randomized, investigator-blinded, dose-ranging study in 17 pediatric patients aged 6 to 30 months. When patient regimen was switched from their usual PEP regimen to PANCREAZE, patients showed similar control of their <sup>(b) (4)</sup> fat malabsorption [see Adverse Reactions (6.1) and Clinical Studies (14)].

Please submit a formal copy of the REMS, PMR/PMC, labeling changes, and transfer of ownership letters formally to the NDA ASAP. Additionally, please send me a courtesy copy of each item by 2pm. If you are unable to send the finalized labeling agreement formally to the NDA today, please send me an email stating you agree to the changes.

Contact me for any questions or concerns.

Thank you.

***Stacy Barley, RN, M.S.N., M.H.A.  
CDR, USPHS Commissioned Corps  
Senior Regulatory Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
CDER/FDA  
(301) 796-2137 (office)  
(301) 796-9905 (fax)  
stacy.barley@fda.hhs.gov***

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**From:** Scott, Ilona [PRDUS] [mailto:IScott1@its.jnj.com]

**Sent:** Friday, April 09, 2010 5:42 PM

**To:** Barley, Stacy

**Subject:** RE: NDA 22523 Panreaze: REMS/REMS Supporting Document

Hi Stacy,

Attached are the REMS and REMS supporting document, in Word, in clean and track changes.

Ilona

Ilona Scott  
Johnson & Johnson Pharmaceutical Research & Development, LLC  
920 US Highway 202  
Raritan, NJ 08869  
Telephone: 908.927.3223  
Cell Phone: 908.229.1830  
Facsimile: 908. 722.5113

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**From:** Barley, Stacy [mailto:Stacy.Barley@fda.hhs.gov]  
**Sent:** Friday, April 09, 2010 1:59 PM  
**To:** Scott, Ilona [PRDUS]  
**Subject:** RE: NDA 22523 Panreaze: labeling Section 14

Hello Ilona,

Thank you for the label below. Please submit the PI and MG formally to the NDA.

Additionally, please send me your PMR/PMCs and REMS for review prior to submitting them formally to the NDA. Thank you.

***Stacy Barley, RN, M.S.N., M.H.A.  
CDR, USPHS Commissioned Corps  
Senior Regulatory Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
CDER/FDA  
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(301) 796-9905 (fax)  
stacy.barley@fda.hhs.gov***

---

**From:** Scott, Ilona [PRDUS] [mailto:IScott1@its.jnj.com]  
**Sent:** Friday, April 09, 2010 1:32 PM  
**To:** Barley, Stacy  
**Subject:** RE: NDA 22523 Panreaze: labeling Section 14

Hello Stacy,

The labeling has been revised with the 1600.

Ilona

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**From:** Barley, Stacy [mailto:Stacy.Barley@fda.hhs.gov]  
**Sent:** Friday, April 09, 2010 12:42 PM  
**To:** Scott, Ilona [PRDUS]  
**Subject:** NDA 22523 Panreaze: labeling Section 14

Hello Ilona,

We are reviewing your label. In reference to the calculation in Section 14, we would like to provide an explanation as to how we arrived at 1600 U lipase/kg/day:

Table 9-12 on Page 86 of the 20-101 Study Report says the mean dose during the run-in period was 2141 U lipase/kg/day.

Multiplying by 0.75 gives: 1606 U lipase/kg/day

This can be approximated to 1600 U lipase/kg/day

We have included the table from study-20-101 as a reference.

Thanks!

***Stacy Barley, RN, M.S.N., M.H.A.  
CDR, USPHS Commissioned Corps***

***Senior Regulatory Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
CDER/FDA  
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(301) 796-9905 (fax)  
stacy.barley@fda.hhs.gov***

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22523

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ORIG-1

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JOHNSON &  
JOHNSON  
PHARMACEUTICA  
L RESEARCH &  
DEVELOPMENT  
LLC

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Pancrelipase Microtablets

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signature** (b) (4)

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/s/

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STACY R BARLEY  
04/12/2010

**From:** Barley, Stacy  
**Sent:** Friday, April 09, 2010 10:41 AM  
**To:** 'Scott, Ilona [PRDUS]'  
**Subject:** NDA 22523 Pancreaze: PMR/PMC comments  
Hello Ilona,

We reviewed your PMR/PMC courtesy copy emailed on yesterday 4/8/10 and have 2 request:

- In your response, PMR 1. Is written as, (b) (4)

(b) (4)

**Please change to: 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.**

No quotation marks needed.

- Additionally, we request the following statement proposed by J&J on 4/8/10 to be included as PMC 10:

Perform in vitro studies to determine the feasibility of administering the contents of Pancreaze (pancrelipase) Delayed-Release Capsules through a gastrostomy tube.

**Final Report Submission by December 30, 2010.**

Please call me if you have any questions. Thank you.

*Stacy Barley, RN, M.S.N., M.H.A.  
CDR, USPHS Commissioned Corps  
Senior Regulatory Project Manager  
Division of Gastroenterology Products  
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stacy.barley@fda.hhs.gov*

Application  
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Submitter Name

Product Name

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NDA-22523

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Pancrelipase Microtablets

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/s/  
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STACY R BARLEY  
04/09/2010

**From:** Barley, Stacy  
**Sent:** Thursday, April 08, 2010 6:43 PM  
**To:** 'Scott, Ilona [PRDUS]'  
**Subject:** NDA 22523 Pancreaze: PMR/PMC discussion and changes to the REMS  
Hello Ilona,

As discussed during our conversation, I am providing you with additional requests for your PRM/PMC communication you plan to submit tomorrow. Please:

- Edit PMC #7 to say: Establish lot release specifications for PCV1 [for the drug substance](#).
- In Reference to the REMS document, clarify who will be responsible for submitting the REMS and the assessment submissions.
- The goal of the REMS should be changed to reflect the following statement (for section I Goals): [To inform patients about the serious risks associated with the use of Pancreaze, including the risk of fibrosing colonopathy and the theoretical risk of transmission of porcine viral disease.](#)
- The PMR (1-3) Dates should reflect the agreed upon Month and Year only (no need to indicate the actual date). The submissions will be due no later than the last day of the month listed.

Thank you.

*Stacy Barley, RN, M.S.N., M.H.A.  
CDR, USPHS Commissioned Corps  
Senior Regulatory Project Manager  
Division of Gastroenterology Products  
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stacy.barley@fda.hhs.gov*

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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STACY R BARLEY  
04/09/2010

**From:** Barley, Stacy  
**Sent:** Thursday, April 08, 2010 1:09 PM  
**To:** 'Lallier, Joe [PRDUS]'  
**Cc:** 'Scott, Ilona [PRDUS]'  
**Subject:** RE: PANCREAZE MT NDA 22-523

**Attachments:** NDA 22523 draft label to Spo

S

(b) (4)

(b) (4)

its

within the label. We used J&J's copy to work off of. Please have your team review these comments and provide us with a courtesy copy addressing the issues ASAP. I had originally asked Ilona to send the label formally to the NDA today however I realize this may not be feasible considering we are still making changes.

General revisions made include:

1. revisions to the highlights section- adverse reaction
2. removal of section 17.4 from table of contents list. This is no longer allowed to be listed as a separate section.
3. section 2.2 grammatical correction.
4. Section 6.1 clarification request (see comment in label). Additionally, please accept all formatting changes to Table 1.
5. The formatted numbering was incorrect in certain sections therefore we have corrected it.
6. Changes made to text in section 10.
7. Clarifying question in section 14 (see comment in label).

Please contact me if you have any questions. Thanks again.

**Stacy Barley, RN, M.S.N., M.H.A.**  
**CDR, USPHS Commissioned Corps**  
**Senior Regulatory Project Manager**  
**Division of Gastroenterology Products**  
**Office of Drug Evaluation III**  
**CDER/FDA**  
**(301) 796-2137 (office)**  
**(301) 796-9905 (fax)**  
**stacy.barley@fda.hhs.gov**

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**From:** Lallier, Joe [PRDUS] [mailto:JLallier@its.jnj.com]  
**Sent:** Thursday, April 08, 2010 12:20 PM  
**To:** Barley, Stacy  
**Cc:** Scott, Ilona [PRDUS]  
**Subject:** PANCREAZE MT NDA 22-523

Dear Stacy,

Hello, this is Joe Lallier from Johnson & Johnson PRD regarding PANCREAZE MT NDA 22-523. Ilona Scott asked that I request labeling comments from you on her behalf so that our team can review and take any necessary action. If you could please forward those comments to me, I would greatly appreciate it.

Please call me at 609.730.6217 if you have any questions or concerns.

Best regards,  
Joe

---

**Joseph A. Lallier, MS, MBA, RAC**

Associate Director, Global Regulatory Affairs - Established Products  
North American Regulatory Leader, Internal Medicine  
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.  
1125 Trenton-Harbourton Road  
Room E12214, Mailstop TE1-1  
Titusville, New Jersey 08560  
T: 609.730.6217  
F: 609.730.2069  
[jlallier@its.jnj.com](mailto:jlallier@its.jnj.com)

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

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/s/

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STACY R BARLEY  
04/09/2010

**From:** Barley, Stacy  
**Sent:** Friday, April 02, 2010 7:42 AM  
**To:** 'Scott, Ilona [PRDUS]'  
**Subject:** RE: NDA 22523 Pancreaze updates - Carton/Container Label  
Good Morning Ilona,

Thank you for the comments below. I shared them with the review team and received the following response:

**All the revisions to the container label and carton labeling look acceptable with the exception of one: the "dose by lipase units" statement should be relocated *beneath* the active ingredient box. There should be no intervening matter between the established name and the strength of the product.**

Please share this with your team members at J&J and let me know if you have any questions. Thanks.

***Stacy Barley, RN, M.S.N., M.H.A.  
CDR, USPHS Commissioned Corps  
Senior Regulatory Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
CDER/FDA  
(301) 796-2137 (office)  
(301) 796-9905 (fax)  
stacy.barley@fda.hhs.gov***

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**From:** Scott, Ilona [PRDUS] [mailto:IScott1@its.jnj.com]  
**Sent:** Thursday, April 01, 2010 10:11 AM  
**To:** Barley, Stacy  
**Subject:** RE: NDA 22523 Pancreaze updates - Carton/Container Label

Stacy,

In response to the Agency's 22 March 2010 facsimile request, attached are representative pdf files for revised carton and container labels for the 16,800 USP lipase unit strength.

1. The print size of the established and proprietary names has been changed so that the established name is printed in letters commensurate with the proprietary name.
2. The active ingredients list is boxed.

3. Each strength (according to Lipase Units) has a unique color to represent each of the four strengths of Pancreaze.
4. The statement, "Dose by Lipase Units," has been reconfigured to read from left to right. The statement, "Dose by Lipase Units," has been placed immediately above the boxed listing of active ingredients, so that it appears in a manner for the viewer to see before reading the list of active ingredients.
5. In accordance with 21 CFR 208.24 (2)(d), the container labels contain the statement, "Attention Pharmacist: Dispense the accompanying Medication Guide to each patient" on the principal display panel.
6. The net quantity statement has been relocated to ensure that there is no intervening matter between the established name and the strength statement.
7. McNeil Pediatrics has been removed from the principal display panel to ensure that the proprietary name and the established name are the most prominent information on the principal display panel.
8. To avoid confusion between hues of red and pink, the color for the 16,800 Lipase Unit strength has been changed to green.

If the changes provided on the attached representative 16,800 strength labels are acceptable to the Agency, they will be incorporated into the other strengths and sent to the Agency.

Kind regards,

Ilona

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**From:** Scott, Ilona [PRDUS]  
**Sent:** Monday, March 22, 2010 6:36 PM  
**To:** Barley, Stacy  
**Subject:** RE: NDA 22523 Pancreaze updates

Thank you for the courtesy copy and updates Stacy. These have been forwarded to the team.

Have a good evening.

Ilona

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**From:** Barley, Stacy [mailto:Stacy.Barley@fda.hhs.gov]  
**Sent:** Monday, March 22, 2010 2:26 PM  
**To:** Scott, Ilona [PRDUS]  
**Subject:** NDA 22523 Pancreaze updates

Hello Ilona,

I hope all is well. I wanted to inform you of an information request faxed to you around 2pm today EDT. I

have attached a courtesy copy of this as well.

<<IR carton and container 3.22.10.pdf>>

Additionally, I wanted to apologize for not issuing labeling changes to you last week. I am waiting for a few more edits to be made and will hopefully send you the PI, MG and REMS by Thursday. It just seemed easier to send everything once all comments have been made.

There are no updates to provide you regarding the CMC submission for "in-use stability". The review has not been finalized however I have not received any additional communication to provide to you regarding the submission at this point.

I have not gotten much feedback regarding the transition plan. The comment I did receive was positive. I requested other team members to provide me with comments as soon as possible.

Please let me know if you have any questions.

***Stacy Barley, RN, M.S.N., M.H.A.  
CDR(sel), USPHS Commissioned Corps  
Regulatory Health Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
CDER/FDA  
(301) 796-2137 (office)  
(301) 796-9905 (fax)  
stacy.barley@fda.hhs.gov***

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

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/s/

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STACY R BARLEY  
04/02/2010

**From:** Barley, Stacy  
**Sent:** Wednesday, March 31, 2010 11:22 AM  
**To:** 'Scott, Ilona [PRDUS]'  
**Subject:** NDA 022523 Pancreaze (pancrelipase)/ Communication of PMRs - CMC  
Hello,

Reference is made to the NDA 022523 Pancreaze (pancrelipase) Delayed-Released Capsules. Please see the PMCs below.

Johnson & Johnson NDA 22-523  
Post Marketing Commitments (Product Quality-CMC)  
March 31, 2010

### **Pancreaze Drug Product**

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

#### **Final Report Submission by XXX**

2. Re-evaluate the acceptance criteria for the protease and amylase assays after more experience is gained with the Pancreaze manufacturing process. After **XXX** drug product lots are manufactured, specifications will be re-evaluated and adjusted to reflect manufacturing history and capability.

#### **Final Report Submission by XXX**

### **Drug Substance**

3. Develop and validate an infectious assay for PCV1.

#### **Final Report Submission by XXX**

4. Establish lot release specifications for PCV1.

#### **Final Report Submission by XXX**

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

#### **Final Report Submission by XXX**

6. Improve the sensitivity of the qPCR assays used for drug substance release testing in order to provide adequate assurance that released drug substance will not contain EMCV, HEV, PEV-9, Reo1/3, Rota, Influenza, VSV-IND, and VSV-NJ

viruses. Revise the assays, and submit assay validation data, together with acceptance criteria.

**Final Report Submission by XXX**

*Stacy Barley, RN, M.S.N., M.H.A.  
CDR, USPHS Commissioned Corps  
Senior Regulatory Project Manager  
Division of Gastroenterology Products  
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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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STACY R BARLEY  
04/02/2010

**From:** Barley, Stacy  
**Sent:** Monday, March 29, 2010 12:34 PM  
**To:** 'Scott, Ilona [PRDUS]'  
**Subject:** NDA 022523 Pancreaze (pancrelipase)/ Communication of PMRs  
Hello,

Reference is made to the NDA 022523 Pancreaze (pancrelipase) Delayed-Released Capsules. Please be advised that Johnson & Johnson Pharmaceutical Research & Development, LLC

1. Deferred requirement for development of an age appropriate formulation for PANCREAZE (pancrelipase) Delayed-Release Capsules: Develop an age appropriate formulation 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 February 28, 2011.
2. 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.
3. A 10 year, observational study to prospectively evaluate the risk of transmission of selected porcine viruses in patients taking PANCREAZE (pancrelipase) Delayed-Release Capsules

For studies numbered 2 and 3, please submit, to your NDA, a timetable identifying the following milestone dates:

**Protocol Submission Date**  
**Study Initiation Date**  
**Study Completion Date**  
**Final Study Report Submission Date**

Please acknowledge your receipt of this email and contact me if you have any questions. Thank you.

*Stacy Barley, RN, M.S.N., M.H.A.  
CDR, USPHS Commissioned Corps  
Senior Regulatory Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
CDER/FDA  
(301) 796-2137 (office)  
(301) 796-9905 (fax)  
stacy.barley@fda.hhs.gov*

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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STACY R BARLEY  
04/02/2010

**From:** [Barley, Stacy](#)  
**To:** ["Scott, Ilona \[PRDUS\]"](#);  
**Subject:** NDA 022523 Pancreaze: additional Comments for carton and container  
**Date:** Friday, March 26, 2010 1:58:45 PM

---

Hello,

We refer to your New Drug Application (NDA) 022523, submitted on June 23, 2009. We are in the process of reviewing NDA 022523, and have the following comments.

- 1. Per 21 CFR 201.15 and 21 CFR 201.100 - Please add the bolded statements, "Protect from moisture", "Avoid excessive heat" and "Do not refrigerate" to the storage conditions listed.**
- 2. Per Health and Human Services Supply Service Center, Perry Point, Maryland, please omit "NSN 6505-01-289-2005" from the carton and container labels.**

Additionally, please clarify the manufacturing listing on the carton and containers. Of note, the 356 lists J&J at Raritan, NJ, but the labels have manufactured by: Nor mark,.....and then manufactured for: McNeil Pediatrics. What is the relationship?

**Please refer to: 21 CFR 201.1 (h)(5)**

**(5) If the distributor is named on the label, the name shall be qualified by one of the following phrases: "Manufactured for \_\_\_\_\_", "Distributed by \_\_\_\_\_", "Manufactured by \_\_\_\_\_ for \_\_\_\_\_", "Manufactured for \_\_\_\_\_ by \_\_\_\_\_", "Distributor: \_\_\_\_\_", "Marketed by \_\_\_\_\_". The qualifying phrases may be abbreviated.**

**(6) If the packer is identified on the label, the name shall be qualified by the phrase "Packed by \_\_\_\_\_" or "Packaged by \_\_\_\_\_". The qualifying phrases may be abbreviated.**

**If you have any questions, please contact me. Thank you.**

***Stacy Barley, RN, M.S.N., M.H.A.  
CDR, USPHS Commissioned Corps***

***Senior Regulatory Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
CDER/FDA  
(301) 796-2137 (office)  
(301) 796-9905 (fax)  
stacy.barley@fda.hhs.gov***

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22523

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ORIG-1

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JOHNSON &  
JOHNSON  
PHARMACEUTICA  
L RESEARCH &  
DEVELOPMENT  
LLC

-----  
Pancrelipase Microtablets

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STACY R BARLEY  
03/26/2010

**From:** [Barley, Stacy](#)  
**To:** ["Scott, Ilona \[PRDUS\]";](#)  
**Subject:** NDA 022523: REMS  
**Date:** Thursday, March 25, 2010 2:17:08 PM  
**Attachments:** [Comments to Applicant 3.25.10.pdf](#)  
[REMS redline-comments 3.25.10.pdf](#)  
[REMS clean-comments 3.25.10.doc](#)

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Hello,

We refer to your NEW DRUG Application NDA 022523 submitted on June 23, 2009. We have comments regarding your Risk Evaluation and Mitigation Strategies (REMS). We would appreciate a response by close of business March 29, 2010. If you have any questions, please contact me using the information found in the signature block below. Thank you.

***Stacy Barley, RN, M.S.N., M.H.A.***  
***CDR, USPHS Commissioned Corps***  
***Senior Regulatory Project Manager***  
***Division of Gastroenterology Products***  
***Office of Drug Evaluation III***  
***CDER/FDA***  
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***stacy.barley@fda.hhs.gov***

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Full immediately following this page as  
B4 (CCI/TS)

**NDA 022523**

**PANCREAZE (pancrelipase)**

Delayed Released Capsules

Manufactured by:

Marketed and Distributed by:

[Note to sponsor: Clarify relationship between companies, the applicant holder is the responsible party, please correct if needed below.]

**McNeil Pediatrics, a Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.  
c/o Johnson & Johnson Pharmaceutical Research & Development, L.L.C.**

**Route 202, PO Box 300**

**Raritan, NJ 08869-0602**

908-927-3223

## **I. GOALS**

To ensure that the following serious risks are adequately communicated to patients and caregivers:

- The risk of fibrosing colonopathy, which may be mitigated by proper dosing of PANCREAZE; and
- The theoretical risk of transmission of viral disease to patients treated with a porcine-derived pancreatic enzyme product.

## **II. REMS ELEMENTS**

### **A. Medication Guide**

A currently approved Medication Guide will be dispensed with each PANCREAZE Delayed Released Capsules prescription in accordance with 21 CFR 208.24.

To comply with 21 CFR 208.24, sufficient numbers of the Medication Guide will be provided to ensure that a copy can be provided with each dispensed PANCREAZE prescription.

Container and carton labels for PANCREAZE will include an instruction alerting the pharmacist to provide a Medication Guide to each patient to whom the product is dispensed.

One copy of the Full Prescribing Information (which includes a medication guide) will be provided with each bottle of PANCREAZE. The Full Prescribing Information, including the Medication Guide, will be available to download on the Internet at: [www.TOBEDETERMINED](http://www.TOBEDETERMINED).

The Medication Guide is appended to this REMS.

## **B. TIMETABLE FOR SUBMISSION OF ASSESSMENTS**

Ortho-McNeil-Janssen Pharmaceuticals, Inc will submit REMS assessments to FDA 18 months, 3 years and 7 years from the date of initial approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment.

Ortho-McNeil-Janssen Pharmaceuticals, Inc will submit each assessment so it will be received by the FDA on or before the due date.

## FDA Comments for REMS

**Comments to Applicant:**

## 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 Risk Evaluation and Mitigation Strategies (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.

## FDA Comments for REMS

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.

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## FDA Comments for REMS

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,

## FDA Comments for REMS

- 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.

Please let us know if you have any questions.

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

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/s/

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STACY R BARLEY  
03/25/2010

**From:** [Barley, Stacy](#)  
**To:** ["Scott, Ilona \[PRDUS\]";](#)  
**Subject:** NDA 022523: PI and MG comments  
**Date:** Thursday, March 25, 2010 2:16:15 PM  
**Attachments:** [NDA 22523 draft-labeling-REDLINE-3.25.10.pdf](#)  
[NDA 22523 draft-labeling-CLEAN- 3.25.10.doc](#)

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Hello,

We refer to your NEW DRUG Application NDA 022523 submitted on June 23, 2009. We have comments regarding your label and Medication Guide (MG). Comments pertaining to your Risk Evaluation and Mitigation Strategies (REMS) will be sent in a separate email. Please review the attachments identified below for the PI and MG. We would appreciate a response regarding the labeling and MG changes by close of business March 30, 2010. If you have any questions, please contact me using the information found in the signature block below. Thank you.

***Stacy Barley, RN, M.S.N., M.H.A.***  
***CDR, USPHS Commissioned Corps***  
***Senior Regulatory Project Manager***  
***Division of Gastroenterology Products***  
***Office of Drug Evaluation III***  
***CDER/FDA***  
***(301) 796-2137 (office)***  
***(301) 796-9905 (fax)***  
***stacy.barley@fda.hhs.gov***

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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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STACY R BARLEY  
03/25/2010



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation ODE III**

**DATE:** March 22, 2010

<b>To:</b> Ilona Scott	<b>From:</b> Stacy Barley
<b>Company:</b> Johnson & Johnson Pharmaceutical Research & Development, LLC	Division of Gastroenterology Products
<b>Fax number:</b> 908.722.5113	<b>Fax number:</b> (301) 796-9905
<b>Phone number:</b> 908.927.3223	<b>Phone number:</b> (301) 796-2137
<b>Subject:</b> Pancrease MT NDA 22-523: Information Request	

**Total no. of pages including cover:** 2

**Comments:**

Hello,  
The FDA is in the process of reviewing NDA 22-523. We have the following comments regarding your carton and container labels.

If you have any additional questions, please contact the Regulatory Project Manager, Stacy Barley, at 301-796-2137.

**Document to be mailed:**             YES             NO

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

**If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2120. Thank you.**

Comments for consideration:

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.

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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/

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STACY R BARLEY  
03/22/2010

**From:** Barley, Stacy  
**Sent:** Wednesday, March 17, 2010 12:22 PM  
**To:** 'Scott, Ilona [PRDUS]'  
**Subject:** FW: NDA 22523 Pancreaze: CMC Information Request

Hello Ilona,

We have reviewed the response from J&J regarding the previous CMC question issued on March 15, 2010 (see email below). We are seeking additional clarification to the question therefore will rephrase it. Please provide us with a response to the following CMC information request by close of business March 19, 2010.

**Please clarify whether Nordmark has supplied the Drug Substance for Pancreaze manufacture since 1988. If another Drug Substance manufacturer has been used instead of Nordmark, please indicate the name of the manufacture(s) , the time periods that the drug substance(s) have been used to manufacture Pancreaze. Please confirm that the Pancreaze manufacturing process (e.g. operating parameter ranges, scale, facility, etc) has not changed since 1988.**

Thank you!

*Stacy Barley, RN, M.S.N., M.H.A.  
CDR(sel), USPHS Commissioned Corps  
Regulatory Health Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
CDER/FDA  
(301) 796-2137 (office)  
(301) 796-9905 (fax)  
stacy.barley@fda.hhs.gov*

---

**From:** Barley, Stacy  
**Sent:** Monday, March 15, 2010 1:43 PM  
**To:** 'Scott, Ilona [PRDUS]'  
**Subject:** NDA 22523 Pancreaze: CMC question

Hello Ilona,

We request confirmation with Johnson & Johnson that the manufacturing process has not changed for NDA 22523 Pancreaze. If it has changed, provide a brief description of the change. Additionally, we request confirmation that the drug substance and its manufacturing process has not changed. Thank you.

*Stacy Barley, RN, M.S.N., M.H.A.  
CDR(sel), USPHS Commissioned Corps  
Regulatory Health Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III*

***CDER/FDA  
(301) 796-2137 (office)  
(301) 796-9905 (fax)  
stacy.barley@fda.hhs.gov***

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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STACY R BARLEY  
03/17/2010

**From:** Barley, Stacy  
**Sent:** Tuesday, March 02, 2010 9:24 AM  
**To:** 'Scott, Ilona [PRDUS]'  
**Subject:** NDA 22523 Pancreaze: CMC Information Request

Hello,

In reference to NDA 22523 Pancreaze (pancrelipase):

We refer to your April 27, 2009 submission, containing the chemistry manufacturing and control information and have the following comments and information requests.

Section M.3.2.P.3.5 (Process Validation and/or Evaluation) states that “the manufacturing process for Pancreaze MT capsules will be fully validated prior to commercial launch.” Please provide the process validation protocol for the Pancreaze drug product and any data available from the process validation studies to date.

Please provide us with the information by COB March 5, 2010. Thank you.

***Stacy Barley, RN, M.S.N., M.H.A.  
CDR(sel), USPHS Commissioned Corps  
Regulatory Health Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
CDER/FDA  
(301) 796-2137 (office)  
(301) 796-9905 (fax)  
stacy.barley@fda.hhs.gov***

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

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/s/

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STACY R BARLEY  
03/02/2010



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation ODE III**

**DATE: February 24, 2010**

<b>To:</b> Ilona Scott	<b>From:</b> Stacy Barley
<b>Company:</b> Johnson & Johnson Pharmaceutical Research & Development, LLC	Division of Gastroenterology Products
<b>Fax number:</b> 908.722.5113	<b>Fax number:</b> (301) 796-9905
<b>Phone number:</b> 908.927.3223	<b>Phone number:</b> (301) 796-2137
<b>Subject:</b> Pancrease MT NDA 22-523: Information Request	

**Total no. of pages including cover: 3**

**Comments:**

Hello,

The FDA is in the process of reviewing NDA 22-523. We request additional information pertaining to your submission. Please see the attachment.

If you have any additional questions, please contact the Regulatory Project Manager, Stacy Barley, at 301-796-2137.

**Document to be mailed:**                       YES                      X NO

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1. In Section 6.1 of the proposed label, you have stated that gastrointestinal complaints were reported in 55% of placebo treated patients, and in 30% of Pancreaze treated patients. Please provide the subject identification numbers for the patients that experienced adverse events classified in the Gastrointestinal Disorders System Organ Class.
2. Please present treatment-emergent adverse events that occurred in at least two patients (i.e.,  $\geq 10\%$ ) in either treatment group of Study PNCRLPCYS3001 summarized by System Organ Class and Preferred Term to produce a table like the following:

**Table 1. Treatment-Emergent Adverse Events Occurring in at least 2 Patients (greater than or equal to 10%) in Either Treatment Group of the Placebo-Controlled, Clinical Study of PANCREAZE**

MedDRA Primary System Organ Class Preferred Term	PANCREAZE (N=20)	Placebo (N=20)
<i>System Organ Class 1</i>		
Preferred Term 1	n (%)	n (%)
Preferred Term 2	n (%)	n (%)
.....	.....	.....
.....	.....	.....
Preferred Term n	n (%)	n (%)
<i>System Organ Class 2</i>		
Preferred Term 1	n (%)	n (%)
Preferred Term 2	n (%)	n (%)
.....	.....	.....
.....	.....	.....
Preferred Term n	n (%)	n (%)
....		
....		
<i>System Organ Class n</i>		
Preferred Term 1	n (%)	n (%)
Preferred Term 2	n (%)	n (%)
.....	.....	.....
.....	.....	.....
Preferred Term n	n (%)	n (%)

3. Based on the datasets that you have provided, Patient 011301 of Study PNCRLPCYS3001 received a dose of  $\geq 10,000$  U lipase/kg/day. Please provide information for this patient that includes the dose administered, adverse events as a result of the dose increase, and adverse events and laboratory results during the follow-up period.
4. In Table 11 (page 45) of the PNCRLPCYS3001 Study Report, you have provided the change in coefficient of fat absorption (CFA) from baseline for each treatment group (Pancreaze and Placebo), and the p-value for the difference between the two groups; however, you have not provided the point

estimate and 95% Confidence Interval for the difference between the two groups. Please provide the point estimate and 95% Confidence Interval for the difference between treatment groups of the change in CFA from baseline.

Application  
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Submitter Name

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ORIG-1

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DEVELOPMENT  
LLC

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Pancrelipase Microtablets

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STACY R BARLEY  
02/24/2010



NDA 022523

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.  
920 Route 202 South  
Raritan, New Jersey 08869

ATTENTION: Ilona Scott  
Director, Global Regulatory Affairs

Dear Ms. Scott:

Please refer to your New Drug Application (NDA) dated June 23, 2009, received June 23, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pancrelipase Capsules, 4,200 units, 10,500 units, 16,800 units, and 21,000 units.

We also refer to your November 9, 2009, correspondence, received November 10, 2009, requesting review of your proposed proprietary name, Pancreaze. We have completed our review of the proposed proprietary name, Pancreaze and have concluded that it is acceptable.

We consider this a final review; however, if approval of the NDA is delayed beyond April 23, 2010 the proposed proprietary name, Pancreaze must be re-evaluated.

If **any** of the proposed product characteristics as stated in your June 26, 2009, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nitin M. Patel, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-5412. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Stacy R. Barley at 301-796-2137.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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

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/s/

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CAROL A HOLQUIST  
02/03/2010

**From:** Barley, Stacy  
**Sent:** Tuesday, January 26, 2010 2:06 PM  
**To:** 'Scott, Ilona [PRDUS]'  
**Subject:** NDA 22523 Pancreaze: Non-clinical Information Request

Hello Ilona,

We have the following non-clinical information request for NDA 22523 Pancreaze:

**Please refer to your September 14, 2009, submission, page four of the table, row three (montan glycol wax). Please provide us with copies of the regulatory references (row 3, column 5) and copies of Lori references of the summary of toxicology information (row 3, column 6) for montan glycol wax.**

Please call me if you have any questions. Thank you.

*Stacy Barley, RN, M.S.N., M.H.A.  
CDR(sel), USPHS Commissioned Corps  
Regulatory Health Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
CDER/FDA  
(301) 796-2137 (office)  
(301) 796-9905 (fax)  
stacy.barley@fda.hhs.gov*

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22523

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STACY R BARLEY  
01/26/2010

**From:** Barley, Stacy  
**Sent:** Friday, January 22, 2010 2:55 PM  
**To:** 'Scott, Ilona [PRDUS]'  
**Subject:** NDA 22523 Tradename (pancrelipase): Clinical Information Request

Hello Ilona,

Could you please respond to the following questions regarding NDA 22523:

(1) Is the to-be-marketed product (TbMP) the same formulation as the currently marketed product (CMP)?

(2) If yes, how long has the CMP been marketed, and since what approximate date has postmarketing data for the product been available?

(3) If no, we would like a brief description of the changes in the formulation.

*Stacy Barley, RN, M.S.N., M.H.A.  
CDR(sel), USPHS Commissioned Corps  
Regulatory Health Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
CDER/FDA  
(301) 796-2137 (office)  
(301) 796-9905 (fax)  
stacy.barley@fda.hhs.gov*

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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STACY R BARLEY  
01/22/2010



NDA 022523

**INFORMATION REQUEST**

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.  
Attention: Ilona J. Scott  
Director, CNS/IM Global Regulatory Affairs  
920 Route 202 South  
Raritan, NJ 08869

Dear Ms. Scott:

Please refer to your New Drug Application (NDA) dated June 23, 2009, received June 23, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Tradename (pancrelipase), Capsules.

We are reviewing your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide a proposed transition plan for the unapproved "Pancrease MT" capsules to Tradename in the U.S. marketplace. Include the following information in your transition plan:
  - a. Describe in detail the period of time during which the unapproved "Pancrease MT" capsules will be withdrawn from the market and Tradename will be introduced. Include the schedule of events associated with each of these activities.
  - b. Identify the steps to be taken to minimize transition time between the unapproved "Pancrease MT" capsules and Tradename.
  - c. Describe the anticipated activities planned to educate key stakeholders about Tradename in order to prevent potential confusion with the unapproved "Pancrease MT" capsules.

If you have any questions, call Stacy Barley, Regulatory Project Manager, at (301) 796-2137.

Sincerely,

*{See appended electronic signature page}*

Brian Strongin, R.Ph., M.B.A.  
Chief Regulatory Health Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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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BRIAN K STRONGIN  
01/08/2010



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation ODE III**

**DATE: December 23, 2009**

<b>To:</b> Ilona Scott	<b>From:</b> Stacy Barley
<b>Company:</b> Johnson & Johnson Pharmaceutical Research & Development, LLC	Division of Gastroenterology Products
<b>Fax number:</b> 908.722.5113	<b>Fax number:</b> (301) 796-9905
<b>Phone number:</b> 908.927.3223	<b>Phone number:</b> (301) 796-2137
<b>Subject:</b> Pancrease MT NDA 22-523: Information Request	

**Total no. of pages including cover: 2**

**Comments:**

Hello,

The FDA is in the process of reviewing NDA 22-523. We request additional information regarding the CMC section of your submission. Please see the attached page.

If you have any additional questions, please contact the Regulatory Project Manager, Stacy Barley, at 301-796-2137.

**Document to be mailed:**             YES             NO

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NDA 22-523  
Information Request  
December 23, 2009

Please address the following issues regarding the drug product quality section of NDA 22-523:

- 1) Your drug product release testing program does not include an assay to monitor the integrity of the microtablets (i.e. friability assay) and an assay to monitor for the process-related impurity simethicone emulsion. A scientific justification including appropriate data must be provided to support the omission of these tests. Alternatively, these tests may need to be implemented to ensure drug product quality.
- 2) Your drug product in-use stability program does not include an evaluation of the product under conditions in which:
  - A. The container closure system has been opened daily by patients over its shelf life.
  - B. The capsules have been exposed to extreme temperatures and moisture for various period of time (i.e. from a few days to up to two weeks).
  - C. The patients have removed multiple capsules from the container closure and used them during the day as needed.Data to support the product's stability under the above conditions should be provided or plans to address these issues should be included in the NDA.
- 3) Your stability program acceptance criteria for RP-HPLC testing only includes four peak areas. The program should include acceptance criteria for all RP-HPLC peaks. Data should be submitted to the NDA to address this deficiency.
- 4) In addition to the USP pancrelipase reference standard your RP-HPLC and USP enzyme assays should include a reference standard that is manufactured by and representative of the drug product process. This standard should be used in all release and stability testing.
- 5) The NDA does not contain information supporting the qualification of the RP-HPLC assay reference standard. This information should be submitted to the NDA.
- 6) The NDA does not contain information regarding shipping procedures and validation studies to ensure that drug product is stable during shipment. This information should be submitted to the NDA.

Application  
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Submission  
Type/Number

Submitter Name

Product Name

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NDA-22523

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LLC

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Pancrelipase Microtablets

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/s/  
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STACY R BARLEY  
12/23/2009

**From:** Barley, Stacy  
**Sent:** Saturday, December 19, 2009 2:47 PM  
**To:** 'Scott, Ilona [PRDUS]'  
**Subject:** NDA 22,523: Nonclinical Information request

**Attachments:** response9142009.pdf  
[Hello Ilona,](#)

We are in the process of reviewing your nonclinical information submitted for NDA 22,523. Please provide the amounts (mg) of the following excipients contained in the capsule in the attached table submitted on September 14, 2009 in Amendment # 0008 in NDA 22,523: gelatin, sodium lauryl sulphate, and sorbitan mono laurate. If necessary, please contact the DMF holder(s) to obtain the specific information. Thank you.



response9142009.p  
df (318 KB)

***Stacy Barley, RN, M.S.N., M.H.A.  
CDR(sel), USPHS Commissioned Corps  
Regulatory Health Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
CDER/FDA  
(301) 796-2137 (office)  
(301) 796-9905 (fax)  
stacy.barley@fda.hhs.gov***

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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STACY R BARLEY  
12/19/2009



NDA 022523

**INFORMATION REQUEST**

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.  
Attention: Ilona J. Scott  
Director, CNS/IM Global Regulatory Affairs  
920 Route 202 South  
Raritan, NJ 08869

Dear Ms. Scott:

Please refer to your New Drug Application (NDA) dated June 23, 2009, received June 23, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Pancreaze (pancrelipase), Capsules.

We are reviewing the clinical pharmacology section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Please compare the baby formula used in your *in vitro* food compatibility study (i.e., Nutricia from Netherland) with each of the baby formulas commercially available in the United States (e.g., Enfamil and Similac) in terms of the following:
  - Composition;
  - pH;
  - Ingredients, if any, that may affect the physical, chemical, or clinical performance of your product.
2. Please provide us with the results of your analysis and the rationale, including supporting data, for your conclusion that comparable food compatibility results will be seen regardless of the particular baby formula used.

If you have any questions, call Stacy Barley, Regulatory Project Manager, at (301) 796-2137.

Sincerely,

*{See appended electronic signature page}*

Donna Griebel, M.D.  
Director  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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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DONNA J GRIEBEL  
12/10/2009



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation ODE III**

**DATE: July 22, 2009**

<b>To:</b> Ilona Scott	<b>From:</b> Stacy Barley
<b>Company:</b> Johnson & Johnson Pharmaceutical Research & Development, LLC	Division of Gastroenterology Products
<b>Fax number:</b> 908.722.5113	<b>Fax number:</b> (301) 796-9905
<b>Phone number:</b> 908.927.3223	<b>Phone number:</b> (301) 796-2137
<b>Subject:</b> Pancrease MT NDA 22-523: Information Request	

**Total no. of pages including cover: 1**

**Comments:**

Hello,

The FDA is in the process of reviewing NDA 22-523. We request additional information pertaining to your June 2, 2009 non-clinical information submission, section 2.6.6 toxicology written summary, Table 2 (page 7). You listed regulatory references, for example "GRAS listed" and "SCOGS database". You also provided the maximum mg/capsule in each microtablet core product (as indicated in table 2). Please provide us with the maximum allowance of mg/capsule as indicated in each regulatory reference. If the daily intake of any excipient is greater than the regulatory reference maximum allowance, please justify.

If you have any additional questions, please contact the Regulatory Project Manager, Stacy Barley, at 301-796-2137.

**Document to be mailed:**                       YES                      X NO

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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/

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STACY R BARLEY  
10/21/2009  
verbal and faxed



NDA 022523

**INFORMATION REQUEST**

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.  
Attention: Iona J. Scott  
Director, CNS/IM Global Regulatory Affairs  
920 Route 202 South  
Raritan, NJ 08869

Dear Ms. Scott:

Please refer to your June 23, 2009, New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tradename (pancrelipase) Capsules.

We are reviewing your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your application.

**RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

Section 505-1 of the FDCA authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Tradename (pancrelipase) Capsules and other porcine-derived pancreatic enzyme products (PEPs) to ensure that the benefits 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.

Your proposed REMS must include the following:

**Medication Guide:** As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Tradename (pancrelipase) Capsules poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Tradename (pancrelipase) Capsules. FDA has determined that Tradename (pancrelipase) Capsules is a product for which patient labeling could help prevent serious adverse effects, has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use

Tradename (pancrelipase) Capsules, and that the Medication Guide is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Tradename (pancrelipase) Capsules.

**Timetable for Submission of Assessments:** The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than by 18 months, 3 years, and in the 7th year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Your proposed REMS submission should include two parts: a "Proposed REMS" and a "REMS Supporting Document." Attached is a template for the Proposed REMS that you should complete with concise, specific information (see Appendix A). Once FDA finds the content acceptable and determines that the application can be approved, we will include these documents as an attachment to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS Supporting Document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

Your assessment of the REMS should include an evaluation of:

- a. Patients' understanding of the serious risks of Tradename (pancrelipase) Capsules.
- b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
- c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.

Before we can continue our evaluation of NDA 022523, you will need to submit the proposed REMS to this application.

Under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. You should submit marked up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide.

We recommend the following language dependent 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.”

Prominently identify the proposed REMS submission with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 022523  
PROPOSED REMS**

Prominently identify subsequent submissions related to the proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 022523  
PROPOSED REMS-AMENDMENT**

If you do not submit electronically, please send 5 copies of your REMS-related submissions.

If you have any questions, please contact Stacy Barley, Regulatory Project Manager, at (301)796-2137.

Sincerely,

*{See appended electronic signature page}*

Joyce Korvick, M.D., M.P.H.  
Deputy Director for Safety  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosures:

Appendix A - REMS Template

Appendix B – REMS Supporting Document Template

## **Appendix A: Medication Guide REMS Template**

**Application number TRADE NAME (DRUG NAME)**

Class of Product as per label

Applicant name

Address

Contact Information

### **RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

#### **I. GOAL(S):**

List the goals and objectives of the REMS.

#### **II. REMS ELEMENTS:**

##### **A. Medication Guide**

*If a Medication Guide is included in the proposed REMS, include the following:*

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

##### **B. Timetable for Submission of Assessments**

For products approved under an NDA or BLA, specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments shall be no less frequent than by 18 months, 3 years, and in the 7<sup>th</sup> year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

## **Appendix B: Medication Guide REMS Supporting Document Template**

This REMS Supporting Document should include the following listed sections 1 through 6. Include in section 4 the reason that the Medication Guide proposed to be included in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Table of Contents
2. Background
3. Goals
4. Supporting Information on Proposed REMS Elements
  - a. Medication Guide
  - b. Timetable for Submission of Assessments of the REMS (for products approved under an NDA or BLA)
5. REMS Assessment Plan (for products approved under an NDA or BLA)
6. Other Relevant Information

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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Pancrelipase Microtablets

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/s/  
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JOYCE A KORVICK  
09/24/2009



NDA 022523

**GENERAL ADVICE**

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.  
Attention: Iona J. Scott  
Director, CNS/IM Global Regulatory Affairs  
920 Route 202 South  
Raritan, NJ 08869

Dear Ms. Scott:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tradename (pancrelipase), Capsules.

We have the following comments regarding your proposed labeling:

Highlights of Prescribing Information

1. Each summarized statement should reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
2. 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.
3. 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.
4. 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)).”
5. Tabular format should be used to enhance accessibility of the Dosage and Administration information when there are different dosing regimens for different indications.
6. 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)].

Full Prescribing Information (FPI)

7. The subheading for subsection 8.3 is currently “Lactation” and must be “**Nursing**”

**Mothers**” [21 CFR 201.56 (d)(1)].

8. 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)].

Please address the identified deficiencies/issues and re-submit labeling by November 19, 2009. This updated version of labeling will be used for further labeling discussions.

If you have any questions, call Stacy Barley, Regulatory Project Manager, at (301) 796-2137.

Sincerely,

*{See appended electronic signature page}*

Brian Strongin, R.Ph, M.B.A.  
Chief Regulatory Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22523

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ORIG-1

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JOHNSON &  
JOHNSON  
PHARMACEUTICA  
L RESEARCH &  
DEVELOPMENT  
LLC

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Pancrelipase Microtablets

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/s/  
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BRIAN K STRONGIN  
09/23/2009



NDA 22-523

**MEETING MINUTES**

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.  
920 Route 202 South  
Raritan, New Jersey 08869

Attention: Ilona Scott  
Director, Global Regulatory Affairs

Dear Ms. Scott:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pancrease MT 4, 10, 16 and 20 (pancrelipase) Capsules.

We also refer to the teleconference between representatives of your firm and the FDA on August 6, 2009. The purpose of the teleconference was to discuss the Division of Medication Error Prevention and Analysis's objection to the submitted proposed proprietary name and request a new proposed proprietary name submission.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Nina Ton, Safety Regulatory Project Manager, at (301) 796-1648.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type C  
**Meeting Date and Time:** August 6, 2009; 9:15 – 9:45 AM EST  
**Meeting Location:** WO Bldg 22, RM 5201  
**Application Number:** 22-523  
**Product Name:** Pancrease MT (pancrelipase)  
**Indication:** Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions  
**Sponsor/Applicant Name:** Johnson & Johnson Pharmaceutical Research & Development, L.L.C.  
  
**Meeting Chair:** Denise Toyer  
**Meeting Recorder:** Nina Ton

**FDA ATTENDEES**

Office of Surveillance and Epidemiology (OSE)

Denise Toyer, PharmD, Deputy Director, DMEPA  
Melina Griffis, RPh, Acting Team Leader, DMEPA  
Anne Crandall, PharmD, Safety Evaluator, DMEPA  
Irene Chan, PharmD, Safety Evaluator, DMEPA  
Cheryl Campbell, MS, Safety Regulatory Project Manger, Team Leader  
Nina Ton, PharmD, Safety Regulatory Project Manager

Office of Drug Evaluation III

Julie Beitz, MD, Director

Division of Gastroenterology Products (DGP)

Donna Griebel, MD, Director  
Anne Pariser, MD, Acting Deputy Director  
Maria Walsh, RN, MS, Acting Associate Director for Regulatory Affairs  
Tamal Chakraborti, PhD, Pharm/Tox Reviewer  
Jane Bai, PhD, Clinical Pharmacology Reviewer  
Marjorie Dannis, MD, Medical Officer  
Anil Rajpal, MD, Acting Medical Officer Team Leader  
Wei Guo, PhD, CMC Reviewer  
Ali Niak, MD, Medical Officer  
Howard Anderson, PhD, CMC Reviewer  
Emanuela Lacana, PhD, Acting CMC Team Leader  
Stacy Barley, RN, MSN, MHA, Regulatory Project Manger  
Elizabeth Ford, RN, Regulatory Project Manager

**SPONSOR ATTENDEES**

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

Andrew E. Mulberg, MD, Compound Development Team Leader

Steven A. Silber, MD, Vice President, Established Products

Donna Panasewicz, Vice President, Global Regulatory Affairs, Established Products

Ilona Scott, Director, Global Regulatory Affairs

Linda Carter, Senior Director, Global Regulatory Affairs

Nancy Micalizzi, Associate Director, CMC Regulatory Affairs

<sup>(b) (4)</sup> [REDACTED], Regulatory Affairs Consultant

Christina Estabrook, Group Product Director, Ortho McNeil Janssen Pharmaceuticals, Inc.

Dorothy Linvill-Neal, Head, Global Trademark Development, Johnson & Johnson Pharmaceutical Services

Valerie Donnelly, Director, Global Trademark Development, Johnson & Johnson Pharmaceutical Service

**BACKGROUND:**

The Division of Medication Error Prevention and Analysis (DMEPA) has evaluated the proposed proprietary name Pancrease MT for NDA 22-523 and found the name unacceptable. The proposed name contains the USAN (United States Adopted Name) stem “ase”. In addition, the name contains the modifier, MT with the #'s “4”, “10”, “16”, and “20”.

**MEETING OBJECTIVES:**

- Discuss DMEPA’s objection to the proposed proprietary name
- Discuss the issues identified with the proposed name
- Request a new proprietary name submission

**DISCUSSION POINTS**

- FDA conveyed to J&J that the proposed proprietary name “Pancrease MT” was considered unacceptable since it contains the USAN stem “ase”. Specifically, FDA is supporting the USAN policy which states that incorporation of a USAN stem in proprietary names is not permitted by the USAN Council because it can lead to confusion between proprietary and established names. FDA informed J&J that this policy was being applied consistently across all proprietary name reviews for drug products in all Offices of New Drugs Review Divisions, not just DGP.
- J&J acknowledged FDA’s policy and inquired on the acceptability of an alternative proposed proprietary name “Pancrease” by changing the letter “s” in Pancrease to the letter “z”. The new name proposal seemed reasonable to FDA, however, it was conveyed that the proposed name would need to undergo a full risk assessment. FDA advised the applicant to submit a new proprietary name review request.
- FDA conveyed to J&J that the use of the modifier “MT” in the proposed proprietary name would be considered unacceptable since it is ambiguous and does not convey any meaningful information about the drug product. Additionally, the numerical modifiers “4”, “10”, “16” and “20” are misleading since these do not represent the strength of all active ingredients in Pancrease. J&J conveyed concern regarding the removal of the modifier “MT” and asked to have another teleconference in the near future to discuss the matter further and to obtain additional guidance and clarification from the FDA. In conclusion, FDA conveyed to J&J that data would be required to support the use of the modifier “MT” and that it should be submitted as part of the new proprietary name request.

**DECISIONS (AGREEMENTS) REACHED:**

The sponsor agreed to withdraw the name “Pancrease MT” and submit a new name for review by DMEPA.

**ACTION ITEMS:**

- None

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/s/  
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CAROL A HOLQUIST  
09/02/2009



NDA 022523

**FILING COMMUNICATION**

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.  
Attention: Iona J. Scott  
Director, CNS/IM Global Regulatory Affairs  
920 Route 202 South  
Raritan, NJ 08869

Dear Ms. Scott:

Please refer to your new drug application (NDA) dated June 23, 2009, received June 23, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Tradename (pancrelipase), capsules.

We also refer to your submissions dated April 27, 2009, May 28, 2009, June 2, 2009, June 26, 2009, July 24, 2009, August 10, 2009, August 13, 2009, and August 24, 2009.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Standard**. Therefore, the user fee goal date is **April 23, 2010**.

We are reviewing your application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by February 25, 2010.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

## **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We note that you have submitted pediatric studies with this application for pediatric patients' age 6 months to 30 months and 7 years to less than 18 years. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for these age groups.

If you have any questions, call Stacy Barley, Regulatory Project Manager, at (301) 796-2137.

Sincerely,

*{See appended electronic signature page}*

Brian Strongin, R.Ph., M.B.A.  
Chief Regulatory Health Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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BRIAN K STRONGIN  
09/01/2009

# MEMORANDUM OF TELECON

DATE: August 17, 2009

APPLICATION NUMBER: NDA 022523

**BETWEEN:**

Name: Donna Panasewicz, Vice President Global Regulatory Affairs  
Bruce Ruoff, Preclinical  
Karen Futterknecht, Regulatory Affairs Consultant  
Phone: 1-888-627-7005 code 434488  
Representing: Johnson & Johnson Pharmaceutical Research & Development, LLC

**AND**

Name: David Joseph, Ph.D., Acting Pharmacology Team Leader  
Ke Zhang, Ph.D., Pharmacology Reviewer  
Anil Rajpal, M.D., Clinical Team Lead  
Stacy Barley, R.N., M.S.N., M.H.A., Regulatory Project Manager  
Division of Gastroenterology Products III

SUBJECT: Discuss Non-clinical Information Request

**Background:**

The Division of Gastroenterology Products issued an information request to Johnson & Johnson Pharmaceutical Research & Development, LLC, on July 17, 2009, pertaining to their June 2, 2009 non-clinical information submission, section 2.6.6 toxicology written summary. The Sponsor left a telephone message on August 10, 2009 seeking additional clarification of the information request and asked for a brief teleconference with the non-clinical reviewers. The teleconference was granted.

**Discussion Points:**

- FDA conveyed to J&J that the non-clinical information submission, section 2.6.6 toxicology written summary, Table 2 (page 7) listed regulatory references, for example "GRAS listed" and "SCOGS database". It was also noted that J&J provided the maximum mg/capsule in each microtablet core product (as indicated in table 2). The FDA asked that J&J provide information regarding the maximum allowance of mg/capsule as indicated in each regulatory reference. If the daily intake of any excipient is greater than the regulatory reference maximum allowance, J&J would need to justify. The FDA wanted to know the maximum dose that would be given per day.
- J&J agreed to create another chart that would identify the maximum milligrams per capsule (which would be identified in a separate column of the chart). They would also include toxicity data.

- The FDA also requests information on all the excipients.

J&J verbalized understating of the discussion points and will begin working on the chart revisions. The Sponsor was also reminded to submit form 3542a to the NDA. The call ended at 1:20 p.m.

Stacy Barley, R.N., M.S.N., M.H.A.

SIGNER'S NAME

TITLE

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22523	----- ORIG 1	----- JOHNSON & JOHNSON PHARMACEUTICA L RESEARCH & DEVELOPMENT LLC	----- Pancrelipase Microtablets

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/s/  
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STACY R BARLEY  
08/28/2009

DAVID B JOSEPH  
08/28/2009



NDA 22-523

**PROPRIETARY NAME REQUEST  
WITHDRAWN**

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.  
920 Route 202 South  
Raritan, NJ (b) (4)

ATTENTION: Ilona J. Scott, Director  
Director, CNS/IM Global Regulatory Affairs

Dear Ms. Scott:

Please refer to your New Drug Application (NDA) dated June 23, 2009, received June 23, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pancrelipase Capsules 4,200 units, 10,500 units, 16,800 units and 21,000 units.

We acknowledge receipt of your August 10, 2009 correspondence, on August 10, 2009, notifying us that you are withdrawing your June 26, 2009 request for review of the proposed proprietary name, Pancrease MT. This proposed proprietary name request is considered withdrawn as of August 10, 2009.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, a new request for a proposed proprietary name review should be submitted.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Nina Ton, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-1468. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22523	----- ORIG 1	-----	----- Pancrelipase Microtablets

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/s/

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CAROL A HOLQUIST  
08/13/2009



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation ODE III**

**DATE: August 11, 2009**

<b>To:</b> Ilona Scott	<b>From:</b> Stacy Barley
<b>Company:</b> Johnson & Johnson Pharmaceutical Research & Development, LLC	Division of Gastroenterology Products
<b>Fax number:</b> 908.722.5113	<b>Fax number:</b> (301) 796-9905
<b>Phone number:</b> 908.927.3223	<b>Phone number:</b> (301) 796-2137
<b>Subject:</b> Pancrease MT NDA 22-523: Information Request	

**Total no. of pages including cover: 1**

**Comments:**

Hello,

The FDA is in the process of reviewing NDA 22-523. We request additional information pertaining to your submission:

- 1) Please confirm that the variable "AEDECOD" in the Integrated Summary of Safety AE dataset and in the Study PNCRLPCYS3001 AE dataset is the Preferred Term variable.
- 2) We were unable to locate the original protocol for PNCRLPCYS3001 within the submission. Please provide this as a formal submission to the NDA as general correspondence by close of business August 14, 2009.
- 3) Please submit your Risk Evaluation and Mitigation Strategies (REMS) for review.

If you have any additional questions, please contact the Regulatory Project Manager, Stacy Barley, at 301-796-2137.

**Document to be mailed:**       YES       NO

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/s/  
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STACY R BARLEY

08/11/2009

# DSI CONSULT: Request for Clinical Inspections

**Date:** August 10, 2009

**To:** Tejashri Purohit-Sheth, M.D., Branch Chief, GCP 2  
Khairy Malek, M.D., DSI Reviewer, GCP2  
Division of Scientific Investigations  
Office of Compliance/CDER

**Through:** Ali Niak, M.D., Medical Reviewer, Division of Gastroenterology Products (DGP)  
Anil Rajpal, M.D., Medical Team Leader, DGP

**From:** Stacy Barley, R.N., M.S.N., M.H.A., Regulatory Project Manager, DGP

**Subject:** **Request for Clinical Site Inspections**  
**Pancrease MT (pancrelipase microtablets)**

## **I. General Information**

Application#: **NDA-022523**

Applicant/ Applicant contact information (to include phone/email):

**Johnson & Johnson Pharmaceutical Research & Development**

**Ilona Scott**

**908-927-3223**

**Iscott1@its.jnj.com**

Drug Proprietary Name: **Pancrease MT**

NME or Original BLA (Yes/No): **NCE**

Review Priority (Standard or Priority): **Standard**

Study Population includes < 17 years of age (Yes/No): **Yes**

Is this for Pediatric Exclusivity (Yes/No): **No**

Proposed New Indication: **Pancreatic insufficiency**

PDUFA: **April 23, 2010**

Action Goal Date: **April 23, 2010**

Inspection Summary Goal Date: **March 1, 2010**

DSI Consult

version: 5/08/2008

**II. Protocol/Site Identification**

*Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.*

Site # (Name, Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site 001017 Mathis, Richard K, MD Miller Children’s Hospital 2801 Atlantic Avenue Long Beach, CA 90806	PNCRLPC YS3001	9	Pancreatic insufficiency (b) (4)
Site 001013 Woo, Marilyn S, MD and Platzker, Arnold, MD** Children’s Hospital Los Angeles 4650 Sunset Blvd Mail Stop 83 Los Angeles, CA 90027	PNCRLPC YS3001	8	Pancreatic insufficiency (b) (4)

**III. Site Selection/Rationale**

The above sites were chosen because of the large number of subjects at these sites as compared to the other sites in the study.

**Domestic Inspections:**

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

**International Inspections:**

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.

Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

**IV. Tables of Specific Data to be Verified (if applicable)**

None.

Should you require any additional information, please contact Stacy Barley at 301-796-2137 or Ali Niak, M.D., at 301-796-2156.

Concurrence: (as needed)

Anil Rajpal \_\_\_\_\_ Medical Team Leader  
Ali Niak \_\_\_\_\_ Medical Reviewer  
\_\_\_\_\_ Division Director (for foreign inspection requests or requests for 5  
or more sites only)

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22523	----- ORIG 1	-----	----- PANCREASE MT

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/s/

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STACY R BARLEY  
08/10/2009



NDA 022523

**NDA ACKNOWLEDGMENT**

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.  
Attention: Ilona J. Scott  
Director, CNS/IM Global Regulatory Affairs  
920 Route 202 South  
Raritan, NJ 08869

Dear Ms. Scott:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Pancrease<sup>®</sup> MT (pancrelipase microtablets) Capsule 4,200, 10,500, 16,800 and 21,000 units of lipase

Date of Application: June 23, 2009

Date of Receipt: June 23, 2009

Our Reference Number: NDA 022523

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 22, 2009, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Gastroenterology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, call Stacy Barley, Regulatory Project Manager, at (301) 796-2137.

Sincerely,

*{See appended electronic signature page}*

Stacy Barley, R.N., M.S.N., M.H.A.  
CDR (sel)/USPHS  
Regulatory Health Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Stacy Barley  
7/7/2009 10:24:54 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

**Meeting Type:** Type B  
**Meeting Category:** Pre-NDA  
**Meeting Date and Time:** 3 December 2008, 3 PM  
**Meeting Location:** WO 22, RM 1311  
**Application Number:** IND 74893  
**Product Name:** Pancrease MT  
**Received Briefing Package** 30 October 2008  
**Sponsor Name:** Johnson & Johnson Pharmaceutical Research & Development, L.L.C. (JJPRD)  
**Meeting Requestor:** Ilona Scott, Director, Global Regulatory Affairs  
**Meeting Chair:** Anil Rajpal, M.D.  
**Meeting Recorder:** Elizabeth A.S. Ford, RN  
**Meeting Attendees:**

**FDA Attendees**

Division of Gastroenterology Products

Donna Griebel, M.D., Director  
Anil Rajpal, M.D., Acting Medical Team Leader  
Anne Pariser, M.D., Medical Officer  
Marjorie Dannis, M.D., Medical Reviewer  
David Joseph, Ph.D., Acting Pharmacology Team Leader  
Ke Zhang, Ph.D., Pharmacology Reviewer  
Elizabeth Ford, R.N., Regulatory Health Project Manager  
Diane Monroe, Regulatory Health Project Manager

Division of Clinical Pharmacology and Biopharmaceutics III

Tien-Mien Chen, Ph.D., Clinical Pharmacology Reviewer

Division of Therapeutic Proteins

Wei Guo, Ph.D., Chemistry Reviewer  
Emanuela Lacana, Ph.D., Acting Associate Lab Chief

Office of New Drug Quality Assessment

Tapash Ghosh, Ph.D., Biopharmaceutics Reviewer

Office of Pharmaceutical Science

Stephen E. Langille, Ph.D., Senior Microbiology Reviewer

Office of Translational Science/Division of Biometrics III

Mike Welch, Ph.D., Statistical Team Leader

Freda Cooner, Statistical Reviewer

Pediatric and Maternal Health Staff

Elizabeth Durmowicz, M.D., Medical Officer

Lisa Mathis, M.D., Associate Director

Matthew Bacho, Regulatory Health Project Manager

Division of Regulatory Review Support

Zei Pao Huang, MS, Team Leader, eReview & eData Support

Erin McCray, Computer Scientist

**Sponsor Attendees**

Fisseha Tesfaye, Director

Nancy Micalizzi, Associate Director, CMC Regulatory Affairs

Bruce Ruoff, Director, Preclinical

Andrew Mulberg, M.D., Portfolio Leader

Ilona Scott, Director, Global Regulatory Affairs

Lilian Li, Associate Director, Clinical PK

Steven A. Silber, M.D., VP, PRD

(b) (4)

Lindsay Cobbs, Associate Director GRPI

**1.0 BACKGROUND**

This Type B Meeting was requested by Johnson & Johnson Pharmaceutical Research & Development, L.L.C. (JJPRD) in correspondence to the FDA, dated 18 September 2008, received 18 September 2008, to discuss the format and content of the planned NDA submission. JJPRD currently plans to submit the Pancrease MT NDA in April 2009.

**2.0 DISCUSSION POINTS**

JJPRD questions are shown below in plain font. FDA Preliminary responses are shown in **boldface**. Discussion at the meeting is shown in *bold italics*.

**2.1 Chemistry, Manufacturing, and Controls**

1. A proposal for Label Claim and Product Specifications is outlined in Section 13.1. Are these label claims and specifications, which reflect 100% of the capsule fill and no overage, acceptable to the Agency?

**FDA Response:**

**Yes.**

**Additional Discussion:**

***The sponsor accepted FDA's response, no discussion occurred.***

2. The calculation of lipase activity in stability studies is detailed in Section 13.2. **Is the proposal for calculation of the lipase activity acceptance criterion and of the stability results to be submitted in the NDA acceptable to the Agency?**

**FDA Response:**

Yes.

**Additional Discussion:**

*The sponsor accepted FDA's response, no discussion occurred.*

3. The Stability Program is detailed in Section 13.3. **Does FDA agree with this proposal?**

**FDA Response:**

No, the information provided in the quantitative analysis of drug product using RP-HPLC to assess process-related impurities and product-related substances and impurities (i.e., degradants) is critical. This analysis should be included in the stability program, and appropriate specifications established.

**Additional Discussion:**

*J&JPRD indicated that the reversed phase HPLC method is being run as part of the registration stability program. Results, specifications, and justification of the specifications will be provided in the NDA.*

4. As described in Section 13.2, the original primary stability lots of PANCREASE MT drug product were encapsulated using a (b) (4) % lipase overage, based on use of USP Pancreatin Lipase Reference Standard Lot I. However, the stability results were determined using the subsequent USP Pancreatin Lipase Reference Standards (either Lot I1E327 or Lot J0G363), which show approximately a (b) (4) when compared to Lot I. J&JPRD proposes (b) (4)

Does the Agency agree with this approach?

**FDA Response:**

**No. Statistical data evaluation supporting the shelf-life in NDA should be performed on converted data sets. Alternatively, a scientific justification for the use of non-converted data sets for statistical analysis should be provided. Please be advised that the shelf life of PANCREASE MT should be determined based on real-time/real temperature stability data. Please refer to ICH Guidelines Q5C for guidance on stability studies for protein products.**

**Additional Comment:**

**Please provide the following product quality microbiology (b) (4) in the new drug application:**

- **Microbial limits specifications for release and stability testing**
- **Validation of microbial limits test methodology**

**Please consult USP chapters <61>, <62>, <1111>, and the USP monograph for Pancrelipase Capsules for additional information on (b) (4) its and test methodology.**

**Additional Discussion:**

***JJPRD agreed to provide justification in the NDA for the statistical analysis of non-converted data sets and that extrapolation of data will not be permitted.***

**2.2 Nonclinical Pharmacology/Toxicology Questions**

5. **The nonclinical toxicology studies conducted for PANCREASE MT are outlined in Section 14. The Sponsor proposes to submit these studies to support the filing and approval of our NDA. Detailed tabulated summary tables for nonclinical studies, as described in the format of the Common Technical Document (CTD), Module 2.6.7, will not be included in this NDA submission. Does the Agency agree with this proposal?**

**FDA Response:**

**No, we do not agree. You need to identify all excipients and the amounts of each excipient in the formulation tested in the toxicity studies cited in section 14. These toxicity studies may not be useful for assessing the safety of the to-be-marketed formulation, if the excipient content of the tested formulation was substantially different from the to-be-marketed formulation.**

**Additional toxicity studies of individual excipients in the to-be-marketed formulation may be needed if:**

1. **The formulation used in the toxicity studies did not contain all excipients present in the to-be-marketed formulation.**

or

2. **The to-be-marketed formulation contains a new excipient (i.e., a substance not listed in the FDA/CDER Inactive Ingredients Database) or an excipient with higher levels than listed for GRAS.**

If either of the above conditions (1 or 2) is applicable, then the need for toxicity studies of individual excipients will be determined based on the estimated maximum daily dose. For example, if the estimated maximum daily dose of an excipient exceeds that of any other approved drug product, supporting information such as toxicity studies (published or original reports), regulatory information, and/or information from health authorities (federal or international) will be needed. The needed studies would include chronic toxicology studies in a rodent and nonrodent species, reproductive toxicology, and genetic toxicology.

PEP products are expected to be used as a long-term therapy. Therefore, the presence of any excipient for which human experience is limited to short-term administration would raise a safety concern, and supporting safety information would be needed, as described above.

For information about the need for nonclinical studies of excipients, refer to the following CDER Guidances: "Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs", April 2006, and "Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients", May 2005.

Include detailed tabulated summary tables for nonclinical studies, as described in the format of the Common Technical Document (CTD), Module 2.6.7, in this NDA submission.

**Additional Discussion:**

*JJPRD agreed to submit reports of the toxicity studies using the microtablet formulation which include information on the excipients. However, JJPRD will not submit toxicity studies on formulations different from the to-be-marketed formulation, given that such studies will not be useful for safety assessment of excipients in the to-be-marketed formulation. JJPRD agreed to submit detailed tabulated summary tables for nonclinical studies.*

6. A letter of authorization cross-referencing a proprietary Drug Master File (DMF), DMF (b) (4), for (b) (4) an excipient in our drug product formulation, will be included in this NDA. The (b) (4) DMF (b) (4) contains detailed toxicology information on the safety of this excipient. Does the Agency agree with this proposal?

**FDA Response:**

**Please specify the toxicity studies in the DMF and submit the reports of the toxicity studies if possible.**

**Additional Discussion:**

***JJPRD agreed to confer with the owner of the DMF and request that a list of toxicity studies relevant to the excipient (b) (4) be provided prior to the NDA submission. JJPRD will request that the study reports of the relevant toxicity studies be submitted with the NDA submission directly to the FDA.***

7. In accordance with the FDA's "Guidance for Industry: Exocrine Pancreatic Insufficiency Drug Products-Submitting NDAs" (April 2006), Section IV.B, the Sponsor plans to provide in the NDA a published literature summary of nonclinical pharmacology information, with a bibliography to meet the requirements of 21 CFR 314.50. Does the Agency agree with this proposal?

**FDA Response:**

**We agree.**

**Additional Discussion:**

***The sponsor accepted FDA's response, no discussion occurred.***

**2.3 Human Pharmacokinetics/Bioavailability Questions**

8. The Pharmacokinetic Analysis Plan for Study PNCRLP-CYS-1001 is detailed in Attachment 3. Does the Agency concur with the calculation of the PK parameters from PNCRLP-CYS-1001, as detailed in the Pharmacokinetic Analysis Plan?

**FDA Response:**

**The proposed PK analysis plan (Attachment 3) appears acceptable. Please make sure that the calculation for percent recovery of exogenous lipase separates the exogenous lipase recovered in duodenum from that recovered in stomach.**

**Additional Discussion:**

***The sponsor accepted FDA's response, no discussion occurred.***

9. Based on the 16 January 2008 End-of-Phase 2 Meeting (Attachment 1B), the Agency concurred that the USP in vitro dissolution data, in combination with the Phase 1 and 3 clinical trial results, can be used to support interchangeability of PANCREASE MT capsules (i.e., MT 4.2, 10.5, 16.8, and 21). At this time, the Sponsor intends to further define the objectives of this interchangeability claim, and to provide the agency with additional details on the study design and data analysis plan in support of this claim. With the interchangeability study, the Sponsor wishes to support the claim that:
1. Clinical application approvability of MT capsules of all strengths (i.e., MT 4.2, 10.5, 16.8, and 21), although not all MT strengths are used in clinical trials to demonstrate bioavailability, safety and efficacy (MT 21 is used in the Phase 1 trial, and MT 10.5 and MT 21 are used in the Phase 3 trial).
  2. Various combinations of MT capsule strengths can be used in a clinical setting to administer the appropriate dose (based on lipase units) of the manufactured product strengths to meet the clinical needs of individual patients.

The Sponsor is conducting in vitro dissolution studies using the USP methods on samples generated from each strength, using a sample size (N=12 independently generated samples at each strength) appropriately powered based on historically observed experimental variability. The objective is to demonstrate that MT capsules, at all dose strengths, release a consistent and equivalent percent of label lipase activity at 30 minutes as measured by the USP dissolution method. The primary analysis will be pair-wise comparisons across the 4 strengths using the bioequivalence criterion of 80% to 125%. The exploratory analysis will be a single degree of freedom linear contrast to investigate the dose related linear trend across the 4 strengths. This test will address if there is a systematic change in a positive or negative direction across strengths. These data, in conjunction with the Phase 1 and 3 trials results, will support the clinical application approvability of the other strengths (MT 4.2 and MT 16.8).

Does the Agency agree with this proposal?

**FDA Response:**

**According to the guidance document “*Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations*”, when the drug product is in the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients to the strength on which BA or BE testing has been conducted, an *in vivo* BE demonstration of one or more lower strengths can be waived based on dissolution tests and an *in vivo* study on the highest strength.**

**While the proposed strengths MT 4.2, MT 10.5, and MT 16.8 capsules are proportionally similar in terms of lipase, amylase and protease units, MT 21 is not. Based on the submitted information, a Phase I study (PNCRLP-CYS1001) is ongoing with MT 21 where subjects are being dosed with 60,000 Units of lipase/meal and lipase, amylase and protease activities are being determined. It appears that no biostudy is planned with the lower strengths;**

please confirm this. Please also clarify the difference between the “MT 20 capsule” (mentioned on page 71 of the meeting package) and the MT 21 capsule.

In the given scenario, provided all proposed strengths are dose-proportional, lower strengths (MT 4.2, 10.5 and 16.8) can be waived from biostudy based on demonstration of satisfactory dissolution profiles and  $f_2$  values comparing each lower strength with the highest strength (MT 21). However, as MT 21 is not proportional with the lower strengths, either of the following two approaches can be undertaken:

- Conduct a clinical study with MT 4.2 and MT 21 and the middle strengths can be waived based on dissolution profiles and  $f_2$  values.
- Conduct a clinical study with MT 16.5 to get a waiver for the lower strengths MT 10.5 and MT 4.2 based on dissolution profiles and  $f_2$  values. Of course, bioavailability study data on MT 21 will be used to support MT 21.

For methodological aspects of dissolution studies, please see the guidance documents “*SUPAC-IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation*” and “*Dissolution Testing of Immediate Release Solid Oral Dosage Forms*”. An  $f_2$  value between 50 and 100 suggests the two dissolution profiles are similar.

In the meeting package, you stated that you plan to conduct USP dissolution studies on all strengths and the primary analysis will be pair-wise comparisons across the four strengths using the BE criterion of 80 – 125%. We remind you that we look at the  $f_2$  (similarity factor) for biowaivers. Please clarify how you intend to use dissolution data to satisfy the BE criterion of 80 – 125%.

You must demonstrate the ability of the current concentration of the capsules to support dosing in all pediatric age groups. The administration of a portion of a capsule is not acceptable. The combinations of the Pancrease MT capsules administered in their entirety, must be able to accommodate the range of doses recommended for pediatric patients. A lower dosing strength appears to be necessary to provide doses which do not exceed the maximum recommended 2500 lipase units/kg per meal, 10,000 lipase units/kg per day and 4000 lipase units/gram fat per day.

*Additional Discussion:*

*JJPRD clarified the difference in lipase activity between the lower strengths and the highest strength (MT 21) to indicate that the dose proportionality*

*between the strengths is weight-based; in order to achieve the higher dose, the API is sourced from pregnant sows (rather than regular sows) which leads to an increased concentration of lipase. JJPRD verified that both capsule strengths are being used in their pivotal study.*

*JJPRD understood that when a biowaiver is concerned, one must differentiate and compare the two profiles. In addition, from a biopharmaceutical perspective, the f2 comparison should include all 3 enzymes. However, the Clinical Team will need to discuss this internally.*

*Based on consensus guidelines utilized by JJPRD, the sponsor indicated the lower dose MT strength would be appropriate for most children (those >6.7 kg). JJPRD acknowledged support for a weight-based dose, but recognized that it needs additional work. JJPRD was referred to the Guidance for Industry: How to Comply with the Pediatric Research Equity Act, as PREA requires the development of a pediatric formulation for all relevant pediatric subpopulations, which in the case of the PEPs, includes patients as young as 1 month of age. JJPRD was further reminded that a plan for studies in pediatric patients is required at the time of NDA submission. The FDA agreed to review any justification for a waiver or deferral of pediatric studies at the time of submission, and reminded JJPRD that in vitro stability data would need to be provided if they plan to open the capsules and mix the contents of MT capsules with a portion of acidic food (for patients who could not swallow the whole capsules) or mix with formula (for much younger patients, e.g., down to one month old).*

#### 2.4 Clinical and Statistical Questions

10. For PNCRLPCYS3001, the Sponsor plans to submit 2 sets of .xpt files for raw and derived dataset variables separately with corresponding define.pdf files. For Study 20-101, one set of .xpt files will be submitted with raw dataset variables. The Sponsor intends to provide these dataset files in a format that does not follow the Standard Data Tabulation Model (SDTM) format. Two sets of .xpt files that contain raw and derived variables will be submitted for the datasets used to support the Integrated Summary of Safety (ISS).  
Does the Agency agree with this proposal?

**FDA Response:**

**We prefer to receive these dataset files in SDTM format.**

**Additional Discussion:**

*The sponsor accepted FDA's response, no discussion occurred.*

11. For Study PNCRLPCYS3001, the Sponsor does not intend to submit SAS programs for efficacy results.  
**Does the Agency agree with this proposal for the efficacy SAS programs?**

**FDA Response:**

**SAS programs greatly facilitate the review process and hence we strongly recommend you provide SAS programs for efficacy results, and preferably for safety results as well.**

**Additional Discussion:**

***The sponsor accepted FDA's response, no discussion occurred.***

12. The Sponsor plans to provide SAS transport files and define.pdf for Study 20-101, Study PNCRLPCYS3001, and the integrated database.  
Does the Agency agree with this proposal?

**FDA Response:**

**Yes, this is acceptable.**

**Additional Discussion:**

***The sponsor accepted FDA's response, no discussion occurred.***

13. Since integration of data from Studies 20-101 and PNCRLPCYS3001 is not possible due to different endpoints, the Sponsor proposes to submit individual study summaries in the Integrated Summary of Efficacy (ISE). Therefore, there will not be a pooled efficacy analysis.  
Does the Agency agree with this proposal?

**FDA Response:**

**Although individual study summaries should be provided as part of the ISE, it is also necessary to provide a detailed integrated analyses of all relevant data across the individual studies that demonstrate substantial evidence of effectiveness for the claimed indication [see 21 CFR 314.50(d)(v)].**

**We note that Studies 20-101 and PNCRLPCYS3001 both measure change in the Coefficient of Fat Absorption (CFA) as a primary endpoint although the measurement time points differ between the two studies. Analyses of the CFA results across the two studies should be provided in the ISE.**

**Additional Discussion:**

***JJPRD agreed, and intends to use consensus guidelines outlining daily enzyme exposure based on dose to construct appropriate dose exposure categories.***

14. An Integrated Summary of Efficacy (ISE) will be provided in Module 5.3.5.3. A separate Summary of Clinical Efficacy (SCE) will not be provided, but a link from Module 2.7.3 to Module 5.3.5.3 will be provided.  
Is the proposal to submit the ISE in Module 5.3.5.3 and link from Module 2.7.3 acceptable to the Agency?

**FDA Response:**

**Yes, this proposal is acceptable.**

**Additional Discussion:**

***The sponsor accepted FDA's response, no discussion occurred.***

15. An Integrated Summary of Safety (ISS) will be prepared in accordance with 21 CFR 314.50(d)(5)(vi) and will be provided in Module 5.3.5.3. Therefore, a separate Summary of Clinical Safety (SCS) will not be provided in Module 2.7.4, but will be hyperlinked to Module 5.3.5.3.  
Is the proposal to submit the ISS in Module 5.3.5.3 and link from Module 2.7.4 acceptable to the Agency?

**FDA Response:**

**Yes, this proposal is acceptable.**

**Additional Discussion:**

***The sponsor accepted FDA's response, no discussion occurred.***

16. In accordance with 21 CFR 314.50(f)2, the Sponsor plans to submit case report forms for patients who died or discontinued due to an adverse event.

(b) (4)

**FDA Response:**

**Case report forms (CRFs) for all patients who died or discontinued the study, whether believed to be drug related or not, should be included at the time of submission. Any additional CRFs needed to conduct a proper review of the application will need to be available upon request.**

**Additional Discussion:**

***The sponsor accepted FDA's response, no discussion occurred.***

**2.5 Safety Questions**

17. PANCREASE MT Capsules have been marketed and monitored for safety since 1988. PANCREASE™ (beads) were marketed and monitored for safety from 1978 until 2006, when the product was voluntarily withdrawn in 2006. The specific formula of pancrelipase is not always specified by the reporting health care provider in Postmarketing reports. Inasmuch as safety reports prior to 1988 could be unrelated to PANCREASE MT, the Sponsor proposes to include the post-marketing spontaneous data for PANCREASE products from 1988 through 2008 in our NDA submission for PANCREASE MT.  
Does the Agency agree with this proposal?

**FDA Response:**

**No. We request that you include all data. However, it is acceptable to present the safety data separately according to those dates (i.e., pre-1988 and 1988-2008).**

**In the meeting package, you state that you intend to summarize the published literature regarding the safety of your product. Because of the concern of the risk of fibrosing colonopathy with pancreatic enzyme products, we request that you specifically query for fibrosing colonopathy as part of your literature review.**

**Additional Discussion:**

***The sponsor accepted FDA's response, no discussion occurred.***

18. PANCREASE MT has been marketed and monitored for safety since 1988. The Sponsor has no known safety concerns that require enhanced pharmacovigilance with the product when used within labeled instructions. The Sponsor proposes to continue to monitor and assess the benefit-risk ratio of this product as routine pharmacovigilance. A detailed routine pharmacovigilance plan as outlined in Attachment 4 will be provided in Module 1.16 of the NDA. Does the Agency agree with this proposal?

**FDA Response:**

**Yes, this is acceptable.**

**Additional Discussion:**

***The sponsor accepted FDA's response, no (b) (4) discussion occurred.***

19. All studies will be completed and included in the original NDA application. J&JPRD does not anticipate any additional safety data to be provided in the (b) (4) (b) (4) requests a waiver of this requirement.

**Additional Discussion:**

***The sponsor accepted FDA's response, no discussion occurred.***

## 2.6 NDA Format Questions

20. The Sponsor proposes to submit Financial Disclosure Information as outlined in 21CFR 54 for the pivotal trial Study PNCRLPCYS3001 only. The Sponsor does not plan to submit Financial Disclosure Information for PNCRLP-CYS-1001 (Phase 1) or 20-101 (Phase 2) trials.  
Does the Agency agree with this proposal?

**FDA Response:**

**No. Financial Disclosure Information for each of the clinical studies included in your NDA submission including the PNCRLP-CYS-1001 (Phase 1) and 20-101 (Phase 2) trials must be submitted. (See the guidance document “Financial Disclosure by Clinical Investigators” for a broader discussion of this issue.)**

**Additional Discussion:**

*The sponsor accepted FDA’s response, no discussion occurred.*

21. The Sponsor proposes to submit our NDA electronically in accordance with the Final Guidance for Industry: *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Applications and Related Submissions Using the eCTD Specifications* (Issued June 2008).  
Does the Division agree that the proposed content and eCTD format, as outlined in Attachment 5, is acceptable?

**FDA Response:**

**Yes, it is acceptable.**

**Additional Discussion:**

*The FDA recommended the sponsor check the most recent FDA guidance available at <http://www.fda.gov/cder/regulatory/ersr/ectd.htm> before submission.*

22. The Sponsor intends to submit single Portable Document Format (PDF) files for each clinical study. Each study will have an associated Study Tagging File.  
Does the Agency agree with this proposal?

**FDA Response:**

**Yes, it is acceptable.**

**Additional Discussion:**

*The FDA indicated a preference to follow the ICH E3 guidance for Structure and Content of Clinical Study Reports. Granular reports are much easier for reviewers to navigate. Legacy study reports may be sent as single files.*

23. The currently available toolsets used to create SAS transport files may create filenames that contain underscore and capital letter characters.  
Does the Agency agree with this proposal on naming of the SAS transport files?

**FDA Response:**

**This is acceptable.**

**Additional Discussion:**

***The sponsor accepted FDA's response, no discussion occurred.***

**2.7 PREA Questions**

24. According to 21CFR 314.55, the NDA should contain data that are adequate to assess the safety and effectiveness of the drug for the claimed indication in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective. Study 20-101 was conducted in children ages 6 to 30 months. The ongoing clinical Protocol PNCRLPCYS3001 allows for enrollment of pediatric subjects from 7 to 18 years of age. At the 23 July 2007 meeting with the FDA, it was agreed that the literature review that will be submitted in the NDA must be sufficient to support dosing, efficacy, and safety in infants from birth to 6 months of age, as well as the remainder of the pediatric population. Any literature available to support these populations will be provided in the NDA. The Sponsor proposes to fulfill the PREA requirement with Study 20-101, Study PNCRLPCYS3001, and with literature review.  
Does the Agency agree with this proposal?

**FDA Response:**

**Although your proposal to fulfill the PREA requirement for Pancrease MT with Study 20-101, Study PNCRLPCYS3001, and a literature review may be acceptable, we cannot determine if the PREA requirement will be fulfilled until the full NDA submission is reviewed. According to 21 CFR 314.55, an NDA *shall* contain data that are adequate to assess the safety and effectiveness of the drug for the claimed indication in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective. In addition, 21CFR 314.55 states that assessments of safety and effectiveness must be carried out using appropriate formulations for each age group(s).**

**Of Note:**

- **An *in vitro* study must be conducted to evaluate the stability of capsule contents when mixed with a small portion of acidic food. *In vitro* stability study findings must support the method of administration in patients unable to swallow whole capsules.**

- You must demonstrate that the combination of the current strengths of the capsules is able to support dosing recommendations for all (b) (4) iatr (b) (4) istration of a capsule is not acceptable. (b) (4)

(b) (4)

- We will need to evaluate your literature review to determine if dosing, efficacy and safety are supported for the pediatric subpopulations that you have not studied (i.e., patients less than 6 months of age, and patients greater than 30 months to less than 7 years of age).

In your NDA submission, please clarify the age range of patients for which you are seeking an indication, and include a description of your pediatric plan. If you are requesting a deferral or partial waiver in pediatric patients below a certain age (e.g., patients less t (b) (4) ), please provide your rationale in accordance with 21 CFR 314.55.

**Additional Discussion:**

*JJPRD proposed to meet the PREA requirement by extrapolating pediatric effectiveness from the clinical trials and literature to all pediatric subpopulations. The FDA indicated that this will be a review issue, and reminded the sponsor that, in general, extrapolation only applies to efficacy. The sponsor must provide safety and dosing data for all relevant pediatric subpopulations.*

**3.0 ATTACHMENTS AND HANDOUTS**

The attached handout was used during the discussion at the meeting.

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

Linked Applications

Sponsor Name

Drug Name / Subject

-----  
IND 74893

-----  
JOHNSON AND  
JOHNSON  
PHARMACEUTICAL  
RESEARCH AND  
DEVELOPMENT LLC

-----  
PANCREASE MT

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

ELIZABETH A FORD  
12/24/2008



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

IND 74,893

Johnson & Johnson Pharmaceutical Research & Development, LLC.  
Attention: Ilona Scott  
Director, Regulatory Affairs  
920 U.S. Highway 202  
P.O. Box 300  
Raritan, NJ 08869

Dear Ms. Scott:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Pancrease MT Capsules.

Please also refer to the teleconference between representatives of your firm and the FDA on January 16, 2008, to discuss your development plans for Pancrease MT.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-0845.

Sincerely,

*{See appended electronic signature page}*

Maureen Dewey, M.P.H.  
Regulatory Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

**MEMORANDUM OF TELECONFERENCE MINUTES**

**MEETING DATE:** January 16, 2008  
**TIME:** 2:00 PM – 3:00 PM  
**APPLICATION:** IND 74,893  
**DRUG NAME:** Pancrease MT

**MEETING CHAIR:** Anne Pariser, M.D.

**MEETING RECORDER:** Maureen Dewey, M.P.H.

**FDA ATTENDEES:**

Joyce Korvick, M.D., M.P.H., Deputy Director  
Anne Pariser, M.D., Medical Team Leader  
Joanna Ku, M.D., Medical Reviewer  
Tien-Mien Chen, Ph.D., Clinical Pharmacology Reviewer  
Michael Welch, Ph.D., Biometrics Team Leader  
Maureen Dewey, Regulatory Project Manager

**EXTERNAL CONSTITUENT ATTENDEES:**

Andrew E. Mulberg, M.D., Clinical Leader,  
Ilona Scott, Director, Global Regulatory Affairs  
(b) (4), RPh, Regulatory Affairs Consultant  
David Hilfiker, Associate Director, Global Regulatory Policy and Intelligence  
George Chi, Ph.D., Senior Director, Clinical Biostatistics  
Lillian Li, Ph.D., PK/PD Leader, Clinical Pharmacology  
Steven Piccoli, Ph.D., Principal Scientist, Global Biomarker Lead, Preclinical Development  
Steven Silber, MD, FACP, Vice President, Therapeutic Area Head, Mature Products  
Linda Ling-Ning Chang, Pharm.D., Sr PK/PD Scientist, Clinical Pharmacokinetics  
Robert An, Ph.D., Sr. Manager, Clinical Biostatistics

**BACKGROUND:**

J&J requested a Type B End of Phase 2 Meeting to obtain FDA input and concurrence on the proposed study designs of the planned Clinical Pharmacology and Clinical Studies to support submission of a new drug application for Pancrease MT.

**ATTACHMENTS/HANDOUTS:**

J&J Discussion Guide  
DGP Hand-out

## **Human Pharmacokinetics and Bioavailability**

1. Based on our 23 July 2007 meeting with the Division, we plan to conduct a Phase I intubation bioactivity/bioavailability study in subjects with severe pancreatic insufficiency, according to the "Guidance for Industry on Exocrine Pancreatic Insufficiency Drug Products – Submitting New Drug Applications," as outlined in the protocol synopsis (Attachment 1). Does the Division concur?

**FDA Response:**

**Yes.**

2. We believe that the proposed study fulfils the requirement for the bioactivity study of Pancrease MT. Does the Division concur?

**FDA Response:**

**Yes; however, we have the following comments regarding the protocol design for the above proposed intubation study. We recommend you:**

1. **Enroll and screen more patients (n >16 eligible patients) in order to obtain 12 analyzable patients. This recommendation is based on high (and unforeseen) failure rate of intubation study procedures.**

**J&J Additional Discussion:**

The protocol will be amended to clarify that a sufficient number of patients will be enrolled to obtain 12 analyzable patients.

2. **Conduct a two-way crossover study design with a washout period of two days between treatment periods, i.e., Treatment 1 (food + water only) vs. Treatment 2 (drug + food + water), in order to:**
  - a. **Eliminate the possibility of secretion of endogenous human pancreatic enzyme due to the stimulating effect of food; and**
  - b. **Calculate more accurately the recovery of exogenous lipase from the dose administered.**

**J&J Additional Discussion:**

We accept this study design; however, we are concerned that the additional burden on patients may impact enrollment and thus the timely completion of the study and submission of the NDA in a timely manner.

The sponsor intends to use endoscopic intubation to minimize patient discomfort and limit withdrawals in a cross-over study requiring multiple intubations. Does the Agency agree?

***FDA Response on 1/16/2008 during the tcon:***

***Yes. Endoscopic placement of the tube is acceptable. We additionally recommend that a double lumen tube be used for collecting aspirates from stomach and duodenum individually.***

**J&J Additional Discussion:**

The sponsor would appreciate Agency's input on specific types of standardized meal recommended for the Phase I bioactivity study.

***FDA Response on 1/16/2008 during the tcon:***

***A high-fat diet similar to what is being proposed for the clinical efficacy study is recommended. Alternatively, a liquid meal would be acceptable as well. A high fat meal may be difficult for intubated patients to eat and swallow. So, the solid food may need to be homogenized first. Please consider that a liquid meal (e.g., 500 mL Ensure Plus) is easier for administering food and Pancrease MT capsules.***

**J&J Additional Discussion:**

The sponsor seeks clarification from the Agency with regards to validated bioanalytical assay methods required for the bioactivity study. We propose to use the clinically validated assays which, although not developed for the same purpose as intended for the sample analysis purpose of this study, are nevertheless the standard of care for physicians in the clinical setting. Does the Agency concur?

***FDA Response on 1/16/2008 during the tcon:***

***No particular bioanalytical method could be specified for the intubation study. Please check the available bioanalytical methods in the published articles. A bioanalytical method is considered acceptable as long as its validation report provides acceptable linearity, accuracy, and precision.***

**Additional Comments:**

***Please provide a conversion factor for the lipase activities obtained from two analytical methods, i.e., 20,000 USP units in a MT20 capsule is equivalent to "X" IU (activity) based on the bioanalytical method used for in vivo intubation study.***

***It is recommended that at the end of intubation study, the stomach be aspirated and analyzed for residual enzyme content as well.***

***J&J agrees to collect the residual of the product in the gastric aspirate at the end of the intubation study.***

3. Use the highest strength, i.e., MT20 capsules, instead of MT10 capsules for this intubation study (protocol synopsis, p. 20, Attachment 1).

*Response on 1/16/2008:*

*J&J agreed.*

4. Demonstrate comparable *in vitro* dissolution data in order to link the rest of the lower strengths to the MT20 capsules.

*Response on 1/16/2008:*

*J&J agreed.*

3. We plan to use information from this Phase 1 intubation bioactivity/bioavailability study, the proposed Phase 3 clinical study, and *in vitro* data (data to be generated as per USP dissolution for Pancrelipase Delayed-Release Capsules) to support interchangeability of Pancrease capsules (i.e., MT 4, MT 10, MT 16, and MT 20), based on our belief that lipase is the most relevant enzyme to study since the accepted primary outcome measure in clinical studies of pancrelipase enzyme products is reduction in steatorrhea (as determined by percent change in COA-fat). Does the Agency agree with this approach?

**FDA Response:**

**Yes.**

*Response on 1/16/2008:*

*J&J agreed.*

4. During the 23 July 2007 meeting, the Division requested review of the protocol prior to study start. We believe the attached synopsis fulfills this request. Does the Division concur?

**FDA Response:**

**Yes.**

*Response on 1/16/2008:*

*J&J agreed.*

## **1.1. Clinical**

1. Our proposed withdrawal design and the sample size for this study are based on the published work of Stern and colleagues, *Am J Gastroenterol* 2000;95(8):1932-8 (Attachment 2). We believe they are sufficient to differentiate Pancrease MT from placebo in terms of COA-fat and to establish the efficacy claim of Pancrease MT. Does the Division concur with our proposal?

### **FDA Response:**

**The general design of the proposed randomized withdrawal clinical study appears to be reasonable. However, we have the following comments:**

1. **Since you are relying on a single clinical efficacy study, the study results must clearly demonstrate substantial evidence of clinical benefit of your product. The results should be highly significant and your assumptions on effect size, type I error, and power may not be adequate to achieve this threshold.**

### **J&J Additional Discussion:**

In order to achieve an outcome with clear evidence of a substantial clinical benefit, a larger sample size would be needed. We propose an adjusted sample size of 18 completers per treatment arm for a total of 36 subjects who complete the study. This sample size will provide an approximate power of 80% at a significance level of 0.0025 two-sided. It represents a 50% increase from our original proposed sample size. See also comment 2a and 2b below.

### ***FDA Response on 1/16/2008:***

***The results of the study will depend on underlying severity of patients enrolled. Conducting a single study in a relatively small population contains inherent risks, and the purpose of our comments was to inform you of the potential pitfalls of your study design and assumptions.***

2. **You are proposing to enroll twenty-five patients with a projected completed patient population of twelve patients per treatment arm. This is a small number of patients, and we are concerned that your study may not be adequately powered to meet the stated objectives of the study. For example:**
  - a. **Our experience to date with similar trials in similar study populations has shown that about one quarter of patients enrolled may have a non-treatment (placebo) coefficient of fat absorption (COA-fat) of 80% or higher, which may lower the mean change in COA-fat in the placebo group (to less than the 34% difference between the active and placebo groups you are projecting).**

**J&J Additional Discussion:**

Our study design is based on the study described in the Stern paper. That study is a randomized study. Therefore, the concern raised in this comment has already been taken into account based on the results of that paper.

- b. The primary efficacy analysis population will include all patients who are randomly assigned into the randomized withdrawal phase and have taken at least one dose of study medication during this phase. Given the small number of patients in each treatment arm, should there be even a small number of drop-outs during this phase; the missing COA-fat results for these patients may adversely affect the overall results for mean change in COA-fat.**

**J&J Additional Discussion:**

Based on the Stern paper, there were 2/38 patients who dropped out. This is around 5% dropout rate. If we use the worst case scenario by imputing the baseline COA-fat value for the missing double blind COA-fat measurement, we effectively reduce the expected treatment difference from 34.9% to 31.2%. The above adjusted sample size has already accounted for these potential early withdrawals.

*FDA Response 1/16/2008:*

*FDA agreed that a treatment difference of 30% or greater is acceptable.*

- 3. Please clarify how you intend to account for missing data, i.e., how do you plan to analyze the data for all randomized patients who withdraw from the randomized withdrawal phase and do not have a COA-fat value during this phase.**

**J&J Additional Discussion:**

We propose to use the completers as the primary efficacy analysis data set, because this will reflect the true treatment effect. However, we will perform the ITT analysis with all randomized patients including those who withdraw early as a sensitivity analysis. In the ITT analysis, patients with missing COA-fat measurements in the double blind withdrawal phase, will have their missing values imputed by their baseline COA-fat measurements.

*FDA Response on 1/16/2008:*

*We do not agree. The ITT should be the primary analysis; additionally we would like to see a completer's analysis to support the primary analysis. Patients who drop out during the randomized phase should not be replaced. You should anticipate some drop-out and account for it. It would be acceptable to impute or replace missing values utilizing the baseline values.*

*J&J agrees not to replace the early drop-outs.*

4. The ANCOVA model used for primary efficacy analysis should include age and treatment groups as factors, and Baseline COA-fat as covariate.

**J&J Additional Discussion:**

Yes. We agree that the ANCOVA model used for primary efficacy analysis as well as all sensitivity analyses and key secondary efficacy analysis will include age, treatment groups as factors AND baseline COA-fat as a covariate, whenever appropriate.

*FDA Response on 1/16/2008:*

*All covariates need to be prespecified in the protocol.*

5. Please confirm that the proposed study will use the to-be-marketed formulation of Pancrease MT. If there are any other studies that will be used to demonstrate the safety or effectiveness of Pancrease MT, please clarify whether they were performed using the to-be-marketed formulation of Pancrease MT or another formulation. If other studies used another formulation of Pancrease MT, please clarify how you intend to link the other formulation(s) to the to-be-marketed formulation.

*Response on 1/16/2008:*

*J&J confirmed that the proposed study will use the TbMP..*

6. Your current Time and Events Schedule table (page 10 of the protocol synopsis) has a single column for Screening (Days -7 to -1), and we are unclear as to the sequence of events that will occur during the Screening Phase of the study. Please expand this column by Day in the Screening Phase to provide greater specificity as to when each of the events/assessments is to occur. Also, please clarify whether the four-day clearance period precedes the three-day average dose calculation period, and whether the high-fat diet will be initiated on the first day of the Open-label Phase, and continue throughout the rest of the study period.

**J&J Addition**

The Time and Events Schedule table (page 10 of the protocol synopsis) has a single column for Screening (Days -7 to -1), and we are unclear as to the sequence of events that will occur during the Screening Phase of the study. Please expand this column by Day in the Screening Phase to provide greater specificity as to when each of the events/assessments is to occur. Also, please clarify whether the four-day clearance period precedes the three-day average dose calculation period, and whether the high-fat diet will be initiated on the first day of the Open-label Phase, and continue throughout the rest of the study period.

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and the three-day average dose calculation period during the study.

*Response on 1/16/2008:*

*Please see attached diagram. FDA communicated our understanding of the sequence of events as illustrated in the attached diagram. J&J concurred and the clearance phase will be removed and patients will be*

*transitioned directly to Pancrease MT during the screening phase. The FDA agreed with this proposal.*

7. Please clarify when a patient will be considered as having entered the study and received at least one dose of the protocol-mandated Pancrease MT, and, therefore, will be included in the Safety Population.

**Additional Discussion:**

*J&J said that "this will be done".*

8. You propose that during the Screening Phase, patients will be off pancreatic enzyme replacement therapy for four days for a "wash-out" or clearance period. Since no COA-fat stool collections would be performed during this time, an alternate proposal would be to consider transitioning patients to Pancrease MT without a washout period and extending the length of the Screening Phase for dose stabilization on Pancrease MT.

(b) (4)

*Response on 1/16/2008:*

*FDA clarified that we are not requesting additional stool samples.*

*J&J stated that the above paragraphs are in error and should be removed.*

9. The protocol synopsis states that "The initial Pancrease MT dose will be based on the average dose taken for the 3 days immediately before entry in to the study. Changes in the open-label phase may be necessary depending on the subject's strict attention to and compliance with a high-fat diet regimen" (page 6, first paragraph). We are concerned that any adjustments to Pancrease MT therapy during the Open Label Run-in Phase would not allow adequate time for patients to achieve steady state on Pancrease MT while consuming the high fat diet, thereby introducing variability in the open-label COA-fat results. Consideration should be given to having patients undergo a longer Pancrease MT dose-stabilization period.

**J&J Additional Discussion:**

We will consider lengthening the dose stabilization period and will discuss this with our investigators.

*Response on 1/16/2008:*

*J&J asked if the stabilization periods could be longer than what is currently proposed. The FDA said yes.*

10. Entry criteria as noted in the Study Population section of the protocol synopsis (page 7) state that patients must be "... stabilized on a diet and dose of pancreatic enzyme supplementation that has provided satisfactory symptom control ..." Please clarify how you will define "satisfactory symptom control." Similarly, in the Time and Events Schedule table (page 11, footnote "a") you state that "...subjects will be instructed to adjust the number of capsules per meal (or snack) to optimize digestion based on clinical signs and symptoms." Please clarify how "optimized digestion" will be defined and how an "optimal dose" will be determined.

**J&J Additional Discussion**

An optimal dose will be assumed when patients report satisfactory symptom control consistent with management of pancreatic insufficiency, e.g., formed stool output and increased stool consistency, absence of abdominal pain or diarrhea, etc. After the open-label phase prior to randomization, a fecal fat collection will be performed requiring COA >80% to enter the randomization phase. Therefore, in light of the fact that data in children and adults demonstrate a lack of absolute correlation between clinical signs and symptoms with improvement in steatorrhea, the critical value will be the baseline COA-fat prior to randomization.

*FDA Response on 1/16/2008:*

*FDA agreed that defining optimal dose by satisfactory clinical symptom scores is reasonable.*

11. Specify whether patients will be permitted to take medications that change the gastric pH (e.g., proton pump inhibitors or H2-blockers) during the study, and whether any adjustments to these medications can be made during the study

**J&J Additional Discussion:**

Stern did not specifically account for the presence or absence of PPIs or acid blockers in their manuscript; Stern did state that, "All 36 adult patients had a history of gastrointestinal and respiratory symptoms. Commonly reported conditions of both adult treatment groups included pancreatic insufficiency, gastroesophageal reflux, mild-to-moderate lung disease requiring occasional-to-

frequent hospitalization for intravenous administration of antibiotics, reactive airway disease, and nasal polyps.”

The sponsor is aware that acid blockers improve efficacy of pancreatic enzyme therapy (b) (4). With this small sample size, randomization may not be sufficient for control of this variable between the two groups. Can the FDA offer their perspective on what recommendations are made regarding medications that change gastric pH during the study?

**FDA Response on 1/16/2008:**

*We recommend that patients do not change their dose of proton pump inhibitors or other acid blocking therapies, if they are on these therapies at study entry. If they are not on these medications, they should not start throughout the duration of the study.*

2. The current study design for the pivotal trial (outlined in Section 10.1.2 and full synopsis in Attachment 3) assesses the efficacy of Pancrease MT10 and MT20, which we believe are capsule strengths representative of all MT dosage strengths based on the comparison in Table 1. Does the Division agree that the protocol design and that these data support the interchangeability of Pancrease MT capsule formulations for the treatment of pancreatic insufficiency?

**FDA Response:**

(b) (4) provided the *in vitro* dissolution data support the lower strength products (see response to Question 2, items 3 & 4).

## 1.2. Regulatory

1. The 26 October 2007 Federal Register notice regarding Exocrine Pancreatic Insufficiency Drug Products (Volume 7, Number 207, p. 60860) notes that the Agency will determine the due diligence of an applicant and will examine the facts and circumstances of the applicant's actions during the drug development and review period to determine whether the applicant exhibited the degree of attention, continuous directed effort, and timeliness as may reasonably be expected. We propose to provide monthly email updates to the FDA Regulatory Project Manager regarding the progress of the clinical program and related NDA activities. Does the Agency concur?

**FDA Response:**

**You do not need to submit monthly emails to demonstrate due diligence.**

2. As noted in the 26 October 2007 Federal Register notice, the FDA intends to continue to exercise its enforcement discretion to allow continued availability of exocrine pancreatic insufficiency drug products until April 28, 2010, if manufacturers have investigational new drug applications (INDs) on active status on or before April 28, 2008, and have submitted new drug applications (NDAs) on or before April 28, 2009.

Our clinical pharmacology and clinical trials are planned to be initiated in March 2008. If it is not possible to complete the studies to meet an April 28, 2009 NDA submission date, can we be assured that, with due diligence being met, Pancrease MT will be allowed to remain on the market until the NDA is approved.

**FDA Response:**

**In a Federal Register Notice published on April 28, 2004 (69 FR 23410), FDA announced that all exocrine pancreatic insufficiency drugs (pancreatic drugs) are new drugs under Section 201(p) of the Federal Food Drug and Cosmetic Act (the Act), requiring approved new drug applications (NDAs) under Section 505 of the Act and 21 CFR Part 314.**

**The April 28, 2004 Federal Register Notice advised that FDA intended to exercise its enforcement discretion until April 28, 2008, as to unapproved pancreatic drugs that were marketed on or before April 28, 2004. To assist manufacturers of these drugs in preparing and submitting documentation to meet NDA requirements, FDA published a final guidance for industry entitled, "Exocrine Pancreatic Insufficiency Drug Products - Submitting NDAs." On October 26, 2007, FDA announced its intention to exercise its enforcement discretion with respect to unapproved pancreatic drugs until April 28, 2010, if the manufacturers have investigational new drug applications on active status on or before April 28, 2009, and have submitted NDAs on or before April 28, 2009. FDA intends to take regulatory action, including but not limited to initiating seizure, injunction, or other judicial or administrative proceedings against manufacturers that are not in compliance with the timeframes set in the October 26, 2007 Federal Register Notice.**

**We recommend that you request periodic milestone meetings, such as pre-NDA meetings, or type C/advice meetings when issues arise in your clinical development program, so that we may assist you, as much as possible, in moving your clinical development program forward.**

**Additional Discussion on 1/16/2008:**

J&J inquired whether submitting a rolling review with submission of even one piece of an NDA would constitute having submitted an NDA even if all components of the NDA were not submitted. FDA stated we would have to clarify this and get back them.

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Linked Applications

Sponsor Name

Drug Name

IND 74893

JOHNSON AND  
JOHNSON  
PHARMACEUTICAL  
RESEARCH AND  
DEVELOPMENT LLC

PANCREASE MT

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

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/s/

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MAUREEN D DEWEY  
01/24/2008

ANNE R PARISER  
01/25/2008