

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-106**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## **STATEMENTS OF CLAIMED EXCLUSIVITY**

In accordance with 21 CFR §314.50(j), Johnson & Johnson Pharmaceutical Research and Development, L.L.C. (J&JPRD) is hereby claiming 5 years of marketing exclusivity for **TRADENAME™** (doripenem for injection) upon approval from the U.S. Food and Drug Administration, under the provision of 21 CFR §314.108(b)(2).

J&JPRD hereby certifies that to the best of its knowledge, doripenem is a New Chemical Entity pursuant to 21 CFR §314.108(a), and FDA has not approved doripenem in any application submitted under section 505(b) of the act after September 24, 1984.

## EXCLUSIVITY SUMMARY

NDA # 22-106

SUPPL # NA

HFD # 520

Trade Name DORIBAX

Generic Name doripenem for injection

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

Approval Date, If Known 10/12/07

### 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

505(b)(1)

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

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

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

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

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

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES

Explain:

!

!

! NO

! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! 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: Susmita Samanta

Title: Regulatory Project Manager

Date: October 12, 2007

Name of Office/Division Director signing form: Wiley Chambers, MD

Title: Acting Director, Division of Anti-Infective and Ophthalmology Products

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

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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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Wiley Chambers  
10/16/2007 10:15:22 PM

## PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

DA/BLA #: 22-106 Supplement Type (e.g. SE5): NA Supplement Number: NA

Stamp Date: 12/13/06 PDUFA Goal Date: 10/12/07

HFD 520 Trade and generic names/dosage form: DORIBAX (doripenem for injection)

Applicant: Johnson and Johnson Pharmaceutical Research and Development, L.L.C.

Therapeutic Class: 1

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? \*

- Yes. Please proceed to the next question.  
 No. PREA does not apply. Skip to signature block.

\* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): \_\_\_\_\_

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 2

Indication #1: Complicated Intra-Abdominal Infection

this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.

No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver  Deferred  Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

### Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population  
 Disease/condition does not exist in children  
 Too few children with disease to study  
 There are safety concerns  
 Other: \_\_\_\_\_

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

**Section B: Partially Waived Studies**

Age/weight range being partially waived (fill in applicable criteria below):

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section C: Deferred Studies**

Age/weight range being deferred (fill in applicable criteria below):

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. 0 Tanner Stage \_\_\_\_\_

Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. 18 Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): 10/12/2012

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age/weight range of completed studies (fill in applicable criteria below):

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

*If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

NDA ~~###-###~~ 22-106

Page 3

This page was completed by:

Susmita Samanta  
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE

(Revised: 10/10/2006)

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: Complicated Urinary Tract Infection

Is this an orphan indication?

Yes. PREA does not apply. Skip to signature block.

No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply:  Partial Waiver  Deferred  Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

**Section A: Fully Waived Studies**

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: \_\_\_\_\_

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section B: Partially Waived Studies**

Age/weight range being partially waived (fill in applicable criteria below)::

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section C: Deferred Studies**

Age/weight range being deferred (fill in applicable criteria below)::

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. 0 Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. 18 Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): 10/12/2012

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age/weight range of completed studies (fill in applicable criteria below):

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

*If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.*

This page was completed by:

Susmita Samanta  
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE

(Revised: 10/10/2006)

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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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Sumathi Nambiar

10/12/2007 04:04:53 PM

## DEBARMENT CERTIFICATION

### DORIPENEM FOR INJECTION

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.

  
\_\_\_\_\_  
Michael Kronig, MD  
Senior Director, Regulatory Affairs  
North American Regulatory Affairs

22 NOV 2006  
Date

## ACTION PACKAGE CHECKLIST

### Application Information

BLA # NDA # 22-106	BLA STN# NDA Supplement # NA	If NDA, Efficacy Supplement Type NA
Proprietary Name: DORIBAX Established Name: Doripenem for Injection Dosage Form: Injection		Applicant: Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
RPM: Susmita Samanta		Division: Anti-Infective and Ophthalmology Products Phone # 301-796-0803
<p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)</p> <p>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 NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p>505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):</p> <p>NA</p> <p>Provide a brief explanation of how this product is different from the listed drug. NA</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p><b>Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.</b></p> <p><input type="checkbox"/> Confirmed                      <input type="checkbox"/> Corrected</p> <p>Date:</p>
❖ User Fee Goal Date		October 12, 2007
❖ Action Goal Date (if different)		October 12, 2007
❖ Actions		
• Proposed action		X AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (specify type and date for each action taken)		X None
❖ Advertising (approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (indicate dates of reviews)		X Requested in AP letter <input type="checkbox"/> Received and reviewed

❖ Application Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 1	
NDAs, BLAs and Supplements: <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2  <input type="checkbox"/> Orphan drug designation	
NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies	
BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies	
NDAs and NDA Supplements: <input type="checkbox"/> OTC drug	
Other:	
Other comments:	
❖ Application Integrity Policy (AIP)	
<ul style="list-style-type: none"> <li>Applicant is 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>Exception for review (<i>file Center Director's memo in Administrative Documents section</i>)</li> <li>OC clearance for approval (<i>file communication in Administrative Documents section</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Yes <input type="checkbox"/> No  <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Public communications (approvals only)	
<ul style="list-style-type: none"> <li>Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Press Office notified of action</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<p>❖ <b>Exclusivity</b></p> <ul style="list-style-type: none"> <li>• NDAs: Exclusivity Summary (approvals only) (<i>file Summary in Administrative Documents section</i>)</li> </ul>	<p>X Included</p>
<ul style="list-style-type: none"> <li>• Is approval of this application blocked by any type of exclusivity? <ul style="list-style-type: none"> <li>• NDAs/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> <li>• NDAs: 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> <li>• NDAs: 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> <li>• NDAs: 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> </li> </ul>	<p>X No      <input type="checkbox"/> Yes</p> <p>X No      <input type="checkbox"/> Yes If, yes, NDA/BLA #      and date exclusivity expires:</p> <p>X No      <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:</p> <p>X No      <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:</p> <p>X No      <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:</p>
<p>❖ <b>Patent Information (NDAs and NDA supplements only)</b></p>	<p>NA</p>
<ul style="list-style-type: none"> <li>• <b>Patent Information:</b> 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>	<p><input type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.</p>
<ul style="list-style-type: none"> <li>• <b>Patent Certification [505(b)(2) applications]:</b> 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> <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>	<p>21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified</p> <p>21 CFR 314.50(i)(1) <input type="checkbox"/> (ii)    <input type="checkbox"/> (iii)</p> <p><input type="checkbox"/> No paragraph III certification Date patent will expire</p>
<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> <li>• [505(b)(2) applications] For <b>each paragraph IV</b> certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.</li> </ul> <p>Answer the following questions for <b>each</b> paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner’s receipt of the applicant’s</p>	<p><input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified</p> <p><input type="checkbox"/> Yes      <input type="checkbox"/> No</p>

notice of certification?

(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 to the next section below (Summary Reviews).

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).

- (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?

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 written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

<p>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 Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</i></p>	
<b>Summary Reviews</b>	
<p>❖ Summary Reviews (e.g., Office Director, Division Director) (indicate date for each review)</p>	<p>10/10/07, 10/12/07, 10/12/07, 10/12/07</p>
<p>❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (indicate date)</p>	
<b>Labeling</b>	
<p>❖ Package Insert</p>	
<ul style="list-style-type: none"> <li>• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	X
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	X
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	X
<p>❖ Patient Package Insert</p>	NA
<ul style="list-style-type: none"> <li>• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	
<p>❖ Medication Guide</p>	NA
<ul style="list-style-type: none"> <li>• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling)</li> </ul>	
<p>❖ Labels (full color carton and immediate-container labels)</p>	
<ul style="list-style-type: none"> <li>• Most-recent division-proposed labels (only if generated after latest applicant submission)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling</li> </ul>	X
<p>❖ Labeling reviews and minutes of any labeling meetings (indicate dates of reviews and meetings)</p>	<p>X DMETS 6/5/07  <input type="checkbox"/> DSRCs  X DDMAC 9/21/07  X SEALD 5/2/07  <input type="checkbox"/> Other reviews  <input type="checkbox"/> Memos of Mtgs</p>

### Administrative Documents

Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) ( <i>indicate date of each review</i> )	10/5/07
❖ NDA and NDA supplement approvals only: Exclusivity Summary ( <i>signed by Division Director</i> )	X Included
❖ AIP-related documents <ul style="list-style-type: none"> <li>Center Director's Exception for Review memo</li> <li>If AP: OC clearance for approval</li> </ul>	
❖ Pediatric Page (all actions)	X 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> )	X Verified, statement is acceptable
❖ Postmarketing Commitment Studies	<input type="checkbox"/> None
<ul style="list-style-type: none"> <li>Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>)</li> </ul>	In the AP letter
<ul style="list-style-type: none"> <li>Incoming submission documenting commitment</li> </ul>	
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	X
❖ Internal memoranda, telecons, email, etc.	X
❖ Minutes of Meetings	
<ul style="list-style-type: none"> <li>Pre-Approval Safety Conference (<i>indicate date; approvals only</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>Pre-NDA/BLA meeting (<i>indicate date</i>)</li> </ul>	<input type="checkbox"/> No mtg 7/27/06
<ul style="list-style-type: none"> <li>EOP2 meeting (<i>indicate date</i>)</li> </ul>	<input type="checkbox"/> No mtg 5/3/04
<ul style="list-style-type: none"> <li>Other (e.g., EOP2a, CMC pilot programs)</li> </ul>	7/7/04
❖ Advisory Committee Meeting	X No AC meeting
<ul style="list-style-type: none"> <li>Date of Meeting</li> <li>48-hour alert or minutes, if available</li> </ul>	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	
<b>CMC/Product Quality Information</b>	
❖ CMC/Product review(s) ( <i>indicate date for each review</i> )	9/9/07
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer ( <i>indicate date for each review</i> )	X None
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Environmental Assessment (check one) (original and supplemental applications)	
<ul style="list-style-type: none"> <li>X Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)</li> </ul>	9/9/07
<ul style="list-style-type: none"> <li><input type="checkbox"/> Review &amp; FONSI (<i>indicate date of review</i>)</li> </ul>	NA
<ul style="list-style-type: none"> <li><input type="checkbox"/> Review &amp; Environmental Impact Statement (<i>indicate date of each review</i>)</li> </ul>	NA
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) ( <i>indicate date of each review</i> )	9/28/07 <input type="checkbox"/> Not a parenteral product
❖ Facilities Review/Inspection	
<ul style="list-style-type: none"> <li>NDAs: Facilities inspections (include EER printout)</li> </ul>	Date completed: 10/9/07 X Acceptable <input type="checkbox"/> Withhold recommendation

❖ BLAs: Facility-Related Documents <ul style="list-style-type: none"> <li>• Facility review (<i>indicate date(s)</i>)</li> <li>• Compliance Status Check (approvals only, both original and supplemental applications) (<i>indicate date completed, must be within 60 days prior to AP</i>)</li> </ul>	NA <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	X Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed
<b>Nonclinical Information</b>	
❖ Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	9/17/07
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input type="checkbox"/> None      10/5/07
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	X No carc
❖ ECAC/CAC report/memo of meeting	
❖ Nonclinical inspection review Summary (DSI)	X None requested
<b>Clinical Information</b>	
❖ Clinical review(s) ( <i>indicate date for each review</i> )	10/11/07, 10/4/07, 9/27/07
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	Safety Review, 10/4/07
❖ Clinical consult reviews from other review disciplines/divisions/Centers ( <i>indicate date of each review</i> )	<input type="checkbox"/> None      9/28/07
❖ Microbiology (efficacy) reviews(s) ( <i>indicate date of each review</i> )	<input type="checkbox"/> Not needed      10/1/07
❖ Safety Update review(s) ( <i>indicate location/date if incorporated into another review</i> )	Located in safety review, dated 10/4/07
❖ Risk Management Plan review(s) (including those by OSE) ( <i>indicate location/date if incorporated into another review</i> )	NA
❖ Controlled Substance Staff review(s) and recommendation for scheduling ( <i>indicate date of each review</i> )	X Not needed
❖ DSI Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input type="checkbox"/> None requested
• Clinical Studies	9/24/07
• Bioequivalence Studies	
• Clin Pharm Studies	
❖ Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None      9/21/07
❖ Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None      9/10/07

**REGULATORY PROJECT MANAGER LABELING REVIEW  
(PHYSICIAN LABELING RULE)**

**Division of Anti-Infective and Ophthalmologic Drug Products**

**Application Number:** NDA 22-106

**Name of Drug:** Doripenem for Injection

**Applicant:** Johnson & Johnson Pharmaceutical Research & Development, LLC

**Material Reviewed:**

**Submission Date:** December 12, 2006

**Receipt Date:** December 13, 2006

**Submission Date of Structure Product Labeling (SPL):** December 12, 2006

**Type of Labeling Reviewed:** WORD/SPL

**Background and Summary**

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

**Review**

The following issues/deficiencies have been identified in the proposed labeling and would be forwarded to the Sponsor for addressing.

**Highlights**

- Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format.
  - After Initial US Approval, delete the hyphen and replace with a colon
  - Insert one line of white space between each major heading in Highlights
  - Remove italics from the Highlights (except )
  - Delete the period after **See 17 for PATIENT COUNSELING INFORMATION**
  - For a new NDA, BLA, or supplement, the revision date should be left blank (e.g., Revised: m/yyyy) at the time of submission and will be edited to the month/year of application or supplement approval.

- The drug name must be followed by the drug's dosage form and route of administration. [See 21 CFR 201.57(a)(2)]. Please revise to:  
Tradename (doripenem) injection for intravenous use

**Full Prescribing Information: Contents**

- A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]

**Full Prescribing Information**

- The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [*see Clinical Pharmacology (12.3)*] not [*See Pharmacokinetics (12.3)*]. Please correct the cross-references throughout the labeling. [See PLR Implementation Guidance]
- The Dosage and Administration section does not include all of the storage information for the drug (e.g, storage before reconstitution).
- Please change 6.2 Adverse Drug Reaction Information from Spontaneous Reports to 6.2 Postmarketing Experience in the FPI and FPI: Contents
  - Under 6.2, add the statement regarding data from postmarketing spontaneous reports recommended in the Adverse Reactions Labeling Guidance, pages 7 and 8.
- Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]
- The "RX only" at the end of the label should be deleted.

**Recommendations**

The Sponsor would be asked to address the identified deficiencies/issues and re-submit labeling by May 18, 2007. This updated version of labeling will be used for further labeling discussions.

Susmita Samanta, M.D.  
Regulatory Project Manager  
Division of Anti-Infective and Ophthalmology Products

Supervisory Comment/Concurrence:

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Frances V. LeSane  
Chief, Project Management Staff

Note: The FDA/CDER/OND SEALD Labeling Team (Bill Pierce, Pharm.D., BCPS) assisted with the development of this Labeling Review.

Drafted: SS/March 1, 2007  
Revised/Initialed:  
Finalized: April 30, 2007  
Filename: c:/data/my documents/22106.labelr.307.doc  
**CSO LABELING REVIEW OF PLR FORMAT**

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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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Susmita Samanta  
5/1/2007 02:18:55 PM  
CSO

Frances LeSane  
5/2/2007 09:49:35 AM  
CSO

**NDA REGULATORY FILING REVIEW**  
**(Including Memo of Filing Meeting)**

NDA # 22-106 Supplement # NA Efficacy Supplement Type SE- NA

Proprietary Name: DORIBAX  
Established Name: Doripenem for Injection  
Strengths: 500 mg/20mL

Applicant: Johnson & Johnson Pharmaceutical Research & Development L.L.C.  
Agent for Applicant (if applicable): NA

Date of Application: December 12, 2006

Date of Receipt: December 13, 2006

Date clock started after UN: NA

Date of Filing Meeting: February 6, 2007

Filing Date: February 9, 2007

Action Goal Date (optional): October 12, 2007

User Fee Goal Date: October 12, 2007

Indication(s) requested: Complicated urinary tract infection (cUTI), Complicated Intra-Abdominal infection (cIAI)

Type of Original NDA: (b)(1)  (b)(2)   
AND (if applicable)

Type of Supplement: (b)(1)  (b)(2)

**NOTE:**

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. 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). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S  P   
Resubmission after withdrawal?  Resubmission after refuse to file?   
Chemical Classification: (1,2,3 etc.) 1  
Other (orphan, OTC, etc.) NA

Form 3397 (User Fee Cover Sheet) submitted: YES  NO

User Fee Status: Paid  Exempt (orphan, government)   
Waived (e.g., small business, public health)

**NOTE:** If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES  NO   
If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES  NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES  NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES  NO   
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES  NO
- Does the submission contain an accurate comprehensive index? YES  NO   
If no, explain:
- Was form 356h included with an authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. agent must sign.**
- Submission complete as required under 21 CFR 314.50? YES  NO   
If no, explain:
- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES
2. This application is an eNDA or combined paper + eNDA YES   
This application is: All electronic  Combined paper + eNDA   
This application is in: NDA format  CTD format   
Combined NDA and CTD formats

- Does the eNDA, follow the guidance?  
(<http://www.fda.gov/cder/guidance/2353fnl.pdf>) YES  NO

**If an eNDA, all forms and certifications must be in paper and require a signature.**

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES   
**If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.**

Additional comments: Some datasets were too large to manipulate and there were duplication of data.

- Patent information submitted on form FDA 3542a? YES X NO

- Exclusivity requested? YES, 5 Years NO

*NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES X NO   
**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**

*NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES X NO

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES X NO

- Is this submission a partial or complete response to a pediatric Written Request? YES  NO X

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES X NO   
**(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)**

*NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES X NO

- PDUFA and Action Goal dates correct in tracking system? YES X NO   
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 64,416

- Are the trade, established/proper, and applicant names correct in COMIS? YES X NO   
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) 5/3/04 NO   
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) 7/27/06 NO   
If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) \_\_\_\_\_ NO X  
If yes, distribute letter and/or relevant minutes before filing meeting.

**Project Management**

- If Rx, was electronic Content of Labeling submitted in SPL format? YES X NO   
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06: Was the PI submitted in PLR format? YES X NO   
If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES X NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES X NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? N/A X YES  NO
- Risk Management Plan consulted to OSE/IO? N/A  YES X NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA X YES  NO

**If Rx-to-OTC Switch or OTC application: NA**

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES  NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES  NO

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? NA YES  NO

**Chemistry**

- Did applicant request categorical exclusion for environmental assessment? YES X NO   
If no, did applicant submit a complete environmental assessment? YES  NO   
If EA submitted, consulted to EA officer, OPS? YES  NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES X NO

- If a parenteral product, consulted to Microbiology Team? YES X NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: 2/6/07

NDA #: 22-106

DRUG NAMES: DORIBAX (doripenem for injection)

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

BACKGROUND: This is a new molecular entity belonging to carbapenem class of antibiotics. This drug is approved in Japan under the name Finibax.

(Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: Janice Soreth, Sumathi Nambiar, Alfred Sorbello, Julie-Ann Crewalk, Thamban Valappil, Scott Komo, Edward Cox, Frederic Marsik, Peter Coderre, Terry Peters, Wendy Schmidt, Chuck Bonapace, Kim Bergman, Rapti Madurawe, Mary Dempsey, Frances LeSane, Yunfan Deng, Lin Qi.

ASSIGNED REVIEWERS (including those not present at filing meeting) :

<u>Discipline/Organization</u>	<u>Reviewer</u>
Medical:	Fred Sorbello, Jim Blank, Julie-Ann Crewalk
Secondary Medical:	Sumati Nambiar
Statistical:	Yunfan Deng, Chris Khedouri
Pharmacology:	Wendy Schmidt
Statistical Pharmacology:	NA
Chemistry:	Lin Qi
Environmental Assessment (if needed):	NA
Biopharmaceutical:	Sarah Robertson
Microbiology, sterility:	John Metcalfe
Microbiology, clinical (for antimicrobial products only):	Peter Coderre
DSI:	Mathew Thomas
OPS:	NA
Regulatory Project Management:	Susmita Samanta
Other Consults:	Andrew Dmytrijuk

Per reviewers, are all parts in English or English translation? YES X NO   
If no, explain:

CLINICAL FILE X REFUSE TO FILE

- Clinical site audit(s) needed? YES X NO   
If no, explain:

• Advisory Committee Meeting needed?	YES, date if known _____	NO	X
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?	N/A	X	YES <input type="checkbox"/> NO <input type="checkbox"/>
CLINICAL MICROBIOLOGY	N/A <input type="checkbox"/>	FILE	X REFUSE TO FILE <input type="checkbox"/>
STATISTICS	N/A <input type="checkbox"/>	FILE	X REFUSE TO FILE <input type="checkbox"/>
BIOPHARMACEUTICS		FILE	X REFUSE TO FILE <input type="checkbox"/>
• Biopharm. study site audits(s) needed? YES			<input type="checkbox"/> NO X
PHARMACOLOGY/TOX	N/A <input type="checkbox"/>	FILE	X REFUSE TO FILE <input type="checkbox"/>
• GLP audit needed?			YES <input type="checkbox"/> NO X
CHEMISTRY		FILE	X REFUSE TO FILE <input type="checkbox"/>
• Establishment(s) ready for inspection?			YES X NO <input type="checkbox"/>
• Sterile product?			YES X NO <input type="checkbox"/>
• If yes, was microbiology consulted for validation of sterilization?			YES X NO <input type="checkbox"/>

ELECTRONIC SUBMISSION: Yes  
Any comments: NA

**REGULATORY CONCLUSIONS/DEFICIENCIES:  
(Refer to 21 CFR 314.101(d) for filing requirements.)**

- The application is unsuitable for filing. Explain why:
- X The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
- No filing issues have been identified.
- X Filing issues to be communicated by Day 74. List (optional):

**ACTION ITEMS:**

1. X Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2.  If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3.  If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. X If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
- 5.X Convey document filing issues/no filing issues to applicant by Day 74.

Susmita Samanta  
Regulatory Project Manager

**APPEARS THIS WAY  
ON ORIGINAL**

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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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Susmita Samanta  
10/5/2007 11:54:52 AM  
CSO

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: 9/21/2007

TO: Susmita Samanta, Regulatory Project Manager  
Sumathi Nambiar, Medical Team Leader  
Wiley Chambers, M.D., Director (Acting), DAIOP  
Division of Anti-Infective and Ophthalmologic Drug Products (DAIOP)

THROUGH: Joseph P. Salewski  
Branch Chief (Acting)  
Good Clinical Practice Branch 2, HFD-47  
Division of Scientific Investigations (DSI)

FROM: Mathew T. Thomas, M.D., GCP 2 Reviewer

SUBJECT: Evaluation of Clinical Inspection.

NDA: #22-106  
APPLICANT: Johnson and Johnson Pharmaceutical Research & Development, LLC.  
DRUG: Doripenem intravenous injection

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATIONS: Complicated intra-abdominal infections  
Complicated urinary tract infections including  
           . pyelonephritis

STAMP DATE: December 13, 2006  
CONSULTATION REQUEST DATE: February 8, 2007  
DIVISION ACTION GOAL DATE: October 13, 2007  
PDUFA DATE: October 13, 2007

**I. BACKGROUND:**

Johnson & Johnson Pharmaceutical Research & Development, LLC., (Henceforth referred to as the sponsor or J&J), submitted data from pivotal studies in support of NDA #22-106 for the investigational drug doripenem intravenous injection.

DAIOP, the review division, requested an inspection of the data generated from seven study-sites (one domestic and six foreign sites). DAIOP requested the inspections because it considered the data essential for the approval of the NDA. In addition, this being a new molecular entity (NME), DSI issued a sponsor monitor inspection.

The results of the FDA inspections are discussed below:

## II. RESULTS (by Site):

Name of CI, IRB, or Sponsor	Protocol #: and # of Subjects:	City, State	Insp. Date	EIR Received Date	Final Classification
Clovis da Cunha, MD	DORI-05: 84	Curitiba-PR, Brazil	July 2 to July 6, 2007	9/12/07	NAI
Jose Cipullo, MD	DORI-05: 68	Sao Jose de Preto-SP, Brazil	July 10 to July 13, 2007	9/14/07	NAI
Claudia Rodriguez, MD	DORI-05: 42	Buenos Aires, Argentina	July 2 to July 6, 2007	9/12/07	NAI
Abel Jasovich, MD	DORI-07: 48	Buenos Aires, Argentina	June 26 to June 29, 2007	9/7/07	NAI
Christopher Lucasti, DO	DORI-07: 23	Somers Point, NJ	April 11 to April 25, 2007	5/22/07	VAI*
Jorge Corral, MD	DORI-08: 35	Mar del Plata, Argentina	July 10 to July 13, 2007	9/12/07	NAI
Oswaldo Malafaia, MD	DORI-08: 80	Curitiba, Brazil	June 25 to June 28, 2007	9/12/07	NAI
Johnson & Johnson – Sponsor	DORI-05 DORI-07 DORI-08	Raritan, NJ	April 25 to May 9, 2007	5/23/07	NAI

### Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI\* = Preliminary Classification – Detailed review of the EIR is ongoing.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-R = Response Requested = Deviation(s) from regulations. See specific comments for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

Pending = DSI has not yet received the EIR from the field investigator or completed the review of the EIR.

1. Clovis da Cunha, MD  
Nossa Senhora de Fatima Av. Visconde  
de guarapuava, 3.077  
Curitiba – PR, Brazil

- a. **What was inspected:** The FDA inspection included a review of the study records of 9 of 84 subjects randomized in protocol #DORI-05 entitled "Phase 3, double-blind, multicenter, randomized study to compare the safety and efficacy of i.v. doripenem and levofloxacin in complicated lower UTI or pyelonephritis."
- b. **Limitations of inspection:** None.
- c. **General observations/commentary:** At the conclusion of this inspection, no deviations were noted within the reviewed documents. No Form FDA 483 was issued to the clinical investigator.
- d. **Assessment of data integrity:** The data from Dr. Cunha's study site appear acceptable.

2. Jose Cipullo, MD, Ph.D.  
Faculdade de Medicina de Sao Jose do Rio  
Preto Av. Brigadeiro Faria Lima 5416  
Sao Jose de Rio Preto-SP, 15090-000  
Brazil

- a. **What was inspected:** The FDA inspection included a review of the study records of 7 of 68 subjects randomized in protocol #DORI-05 entitled "Phase 3, double-blind, multicenter, randomized study to compare the safety and efficacy of i.v. doripenem and levofloxacin in complicated lower UTI or pyelonephritis."
- b. **Limitations of inspection:** None.
- c. **General observations/commentary:** At the conclusion of this inspection, no deviations were noted within the reviewed documents. No Form FDA 483 was issued to the clinical investigator.
- d. **Assessment of data integrity:** The data from Dr. Cipullo's study site appear acceptable.

3. Claudia Rodriguez, MD  
Hospital Argerich, Almirante Brown 240  
1 er Piso Infectologia, C1155ADP  
Ciudad de Buenos Aires, Argentina

- a. **What was inspected:** The FDA inspection included a review of the study records of 10 of 42 subjects' in protocol #DORI-05 entitled "Phase 3, double-blind, multicenter, randomized study to compare the safety and efficacy of i.v. doripenem and levofloxacin in complicated lower UTI or pyelonephritis."
- b. **Limitations of inspection:** None.
- c. **General observations/commentary:** At the conclusion of this inspection, no deviations were noted within the reviewed documents. No Form FDA 483 was issued to the clinical investigator.
- d. **Assessment of data integrity:** The data from Dr. Rodriguez's study site appear acceptable.

4. Abel Jasovich, MD  
Sanatorio Guemes Francisco Acuna de Fiduroa  
Av. Rogue Saenz Peria 811 5°C  
(C1035AAD)  
Buenos Aires, Argentina

- a. **What was inspected:** The FDA inspection included a review of the study records of 10 of 48 subjects' in protocol #DORI-07 entitled "Phase 3, double-blind, multicenter, randomized study comparing the safety and efficacy of i.v. doripenem with meropenem (MEPM) in patients with complicated intra-abdominal infections."
- b. **Limitations of inspection:** None.
- c. **General observations/commentary:** At the conclusion of this inspection, no deviations were noted within the reviewed documents. No Form FDA 483 was issued to the clinical investigator.
- d. **Assessment of data integrity:** The data from Dr. Jasovich's study site appear acceptable.

5. **Christopher Lucasti, DO**  
730 Shore Road  
Sommers Point, NJ 08244-2331

- a. **What was inspected:** The FDA inspection included a review of the study records of all 23 subjects' in protocol #DORI-07 entitled "Phase 3, double-blind, multicenter, randomized study comparing the safety and efficacy of i.v. doripenem with meropenem (MEPM) in patients with complicated intra-abdominal infections."
- b. **Limitations of inspection:** None.
- c. **General observations/commentary:** At the conclusion of this inspection, a Form FDA 483 was issued to the clinical investigator with two objectionable conditions:
  - 1) Protocol deviations included deviations from drug delivery times in 14 subjects, laboratory testing in 9 subjects, follow-up visits for 8 subjects and prohibited antibiotics for 3 subjects and inappropriate consent in 1 subject; and
  - 2) Inadequate drug disposition records for five subjects.

The clinical investigator sent a written response to the Form 483 observations, dated May 9, 2007, and provides explanations for the observations and provides assurances to make voluntary corrections and changes in his procedures to prevent similar violations from not recurring in any ongoing or future studies he conducts.

- d. **Assessment of data integrity:** In general, the data from Dr. Lucasti's site appear acceptable. DSI has not completed a detailed review of this EIR. If DSI changes its opinion regarding the data acceptability from Dr. Lucasti's site, it will send DAIOP an Amendment to this CIS.

6. **Jorge Corral, MD**  
Hospital Interzonal de Agudos Dr. Oscar Alenda  
Juan B. Justo s/n y calle 164  
C7600 Mar del Plata, Argentina

- a. **What was inspected:** The FDA inspection included a review of the study records of 10 of 35 subjects' in protocol #DORI-08 entitled "Phase 3, double-blind, multicenter, randomized study comparing the safety and efficacy of i.v. doripenem with i.v. MEPM in patients with complicated intra-abdominal infections."

- b. **Limitations of inspection:** None.
- c. **General observations/commentary:** At the conclusion of this inspection, no deviations were noted within the reviewed documents. No Form FDA 483 was issued to the clinical investigator.
- d. **Assessment of data integrity:** The data from Dr. Corral's study site appear acceptable.

7. Osvaldo Malafaia, MD  
de Curitiba Ins. de Pesquisas Medicas  
Alameda Augusto Stellfeld 1980  
Curitiba-PR, 80730-000  
Brazil

- a. **What was inspected:** The FDA inspection included an in-depth review of the study records of 3 of 80 subjects' in protocol #DORI-08 entitled "Phase 3, double-blind, multicenter, randomized study comparing the safety and efficacy of i.v. doripenem with i.v. MEPM in patients with complicated intra-abdominal infections."
- b. **Limitations of inspection:** None.
- c. **General observations/commentary:** At the conclusion of this inspection, no deviations were noted within the reviewed documents. No Form FDA 483 was issued to the clinical investigator.
- d. **Assessment of data integrity:** The data from Dr. Malafaia's study site appear acceptable.

8. Johnson & Johnson Pharmaceutical Research & Development, LLC.  
920 U. S. Highway 202, P.O. Box 300  
Raritan, NJ 08869

- a. **What was inspected:** The FDA inspection included a review of the monitoring of study Protocol #s DORI-05, DORI-07, and DORI-08 and focused on the monitoring of studies conducted by the following clinical investigators:

Kallol Chauduri, MD, Ph.D. – USA – DORI-08  
Jose Ci pullo, MD, Ph.D. – Brazil – DORI-05  
Jorge Corral, MD – Argentina – DORI-08  
Clovis da Cuhna, MD – Brazil – DORI-05  
Antonio Freire, MD – Brazil – DORI-07

Abel Jasovich, MD – Argentina – DORI-07  
Christopher Lucasti, MD – USA – DORI-07  
Osvaldo Malafaia, MD – Brazil – DORI-08  
Claudia Rodriguez, MD – Argentina – DORI-05

The inspection reviewed the following: Quality assurance and clinical operations, study monitoring procedures, records and reports, monitoring reports and study drug accountability.

- b. **Limitations of inspection:** None.
- c. **General observations/commentary:** At the conclusion of this inspection, FDA issued a one-item Form FDA 483, Inspectional Observations, to the sponsor for not maintaining adequate drug disposition documentation from at least three of the inspected study sites. The sponsor obtained and provided the missing drug disposition documentation to the FDA investigator prior to the conclusion of the inspection. FDA does not have any additional evidence to dispute the study sites' claims that their hospital staff destroyed the unused drugs.
- d. **Assessment of data integrity:** The sponsor appears to have adequately conducted the studies, and the data generated and submitted by the sponsor in support of the indications in support of NDA #22-106 appear acceptable.

#### IV. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

DSI's recommends that the data generated in support of NDA #22-106 appear acceptable.

*{See appended electronic signature page}*

Mathew T. Thomas, MD.  
Pharmacologist  
GCPB-2, DSI

#### CONCURRENCE:

Supervisory comments:

*{See appended electronic signature page}*

Joseph P. Salewski  
Branch Chief (Acting)  
Good Clinical Practice Branch 2  
Division of Scientific Investigations

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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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Mathew Thomas  
9/21/2007 05:33:47 PM  
MEDICAL OFFICER

Clinical Inspection Summary NDA 22-106 Doripenem

Joseph Salewski  
9/24/2007 08:25:49 AM  
CSO

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** July 27, 2006  
**TIME:** 11:00 A.M.-12:30 P.M.  
**APPLICATION:** 64,416  
**DRUG NAME:** Doripenem for Injection  
**SPONSOR:** Johnson & Johnson Pharmaceutical Research & Development, LLC

### **Participants from the Division of Anti-Infective and Ophthalmology Drug Products:**

Ed Cox, MD, MPH, Deputy Director, Office of Antimicrobial Products  
Janice Soreth, MD, Division Director  
Sumati Nambiar, MD, MPH, Clinical Team Leader  
Janice Pohlman, MD, MPH, Clinical Reviewer  
Alfred Sorbello, DO, Clinical Reviewer  
Wendelyn Schmidt, PhD, Pharmacology-Toxicology Reviewer  
PhD, Pharmacology-Toxicology Reviewer  
Peter Coderre, PhD, Microbiology Reviewer  
Thamban Valappil, PhD, Statistical Team Leader  
Scott Komo, DrPH, Statistical Reviewer  
Arzu Selen, PhD, Deputy Director, Office of Clinical Pharmacology 4  
Charles Bonapace, PharmD, Clinical Pharmacology Reviewer  
Frances LeSane, Chief, Project Management Staff  
Milton Sloan, PhD, Chemistry Reviewer  
Don Duggan II, Regulatory Information Specialist  
Virginia Ventura, Regulatory Information Specialist  
Kerry Snow, MS, Microbiology Reviewer  
Susmita Samanta, MD, Project Manager

### **Participants from J&JPRD:**

Alysia Baldwin-Ferro Director, Global Regulatory Leader  
Robert Flamm, Ph.D. Head Clinical Microbiology, Preclinical Anti-Infectives Team  
Melissa Gannon Assistant Director, Medical Writing  
Catherine Glamkowski Associate Director, Regulatory Affairs  
Karen Grosser, Ph.D. Vice President, Compound Development Team Leader  
Michael Kronig, M.D. Senior Director, Regulatory Affairs  
George Marchesini Associate Director, Regulatory Affairs, Chem-Pharm  
Andrea Masciale, J.D. Director, Regulatory Affairs (FDA Liaison)  
Partha Nandy, Ph.D. Associate Director, Advanced Modeling and Simulation  
Peter Ouyang, Ph.D. Senior Director, Therapeutic Area Head of Statistics  
Kenneth C. Turner, Ph.D. Director, Clinical Pharmacology & Experimental Medicine

### **Peninsula Pharmaceuticals, Inc.**

Ian Friedland, M.D. Senior Director, Clinical Development  
Lily Llorens, Ph.D. Associate Director, Statistical Leader

**BACKGROUND:**

On May 4, 2006, Johnson & Johnson requested a pre-NDA meeting for doripenem. The meeting was granted and scheduled to occur on July 27, 2006. J & J sent the package on June 23, 2006. Responses to the questions posed in the briefing package were sent to the Sponsor on July 26th and the document is attached here for reference.

The Sponsor is planning to submit one NDA in December, 2006 for the indications of complicated Urinary Tract Infections (cUTI) and complicated Intra-Abdominal Infections (cIAI).

**DISCUSSION POINTS:**

After the introduction of the attendees, the following questions were discussed.

Question #5, Microbiology:

The Sponsor stated that the December 2006 cIAI/cUTI NDA will contain:

- Microbiological outcome by MIC in each clinical study report for the pivotal trials in cIAI and cUTI.
- In the June 2007 amendment to the cIAI/cUTI NDA, in the microbiological summary, clinical and microbiologic outcome by MIC evaluations for cUTI, cIAI and NP pooled by indication, and pooled across indications where relevant.

If the data demonstrate a need for indication-specific breakpoints, the Sponsor will consider that.

The Agency stated that breakpoint for one organism may be different for different indications. The Agency will try to review the data submitted in the June, 2007 amendment but cannot promise to complete the review before the action date.

Question #5, Clinical Pharmacology:

The Sponsor plans to submit the time above MIC data for the cIAI, cUTI NDA in an amendment in June, 2007.

The Agency said that will be acceptable.

Question #3, Clinical Pharmacology:

The Sponsor stated that other \_\_\_\_\_ in their labels. The Sponsor wants to include the same information for doripenem.

It was agreed that the Sponsor will submit raw PK datasets for Phase 2 and 3 studies conducted in Japan. The Sponsor mentioned that annotated case report forms were not generated for these studies; however, source data, raw data and analysis are available for auditors.

Question #7, Clinical Pharmacology:

It was agreed that the Sponsor will provide PK parameters within the datasets only for all Phase 1 studies conducted in the Western population. The Sponsor will provide concentration and basic demographic datasets for Phase 1 studies conducted in Japan.

The following question was e-mailed to the Agency on July 20:

Does the Agency agree that if necessary, urinary PK results from 3 Phase 1 studies which will be described within summaries of Biopharmaceutics and Clinical Pharmacology could be provided within the 4-month safety update?

The Sponsor plans to submit data from three Phase 1 studies (DORI1004, DORI1005, and DORI1006) with a urinary PK component in the cIAI/cUTI NDA. So far, urine PK samples have been analyzed for DORI1004 and DORI1006 and the results were not consistent. The Sponsor has not performed the cross validation analysis yet. If the contributing factor is found to be due to the matrix effect, urinary PK results would not be available in December, 2006.

It was agreed that the data can be submitted within 4 months after the submission of the cIAI/cUTI NDA.

The following agreements were made regarding the clinical/statistical questions:

- The Sponsor will provide datasets for each individual study within two weeks of July 27, so that that the Agency can request a random sample of approximately 10-15% of treatment-blinded CRFs for inclusion in the initial NDA submission. The Agency will generate the random sample within 4 weeks of receiving the datasets. (Post-meeting note: The Sponsor sent the datasets on August 4, 2006).
- The Agency agreed to provide comments within this timeframe.
- The Agency agreed to send comments regarding the updated versions of the SAPs for cIAI and cUTI submitted to the Agency in the pre-NDA meeting package by August 4, 2006. (Post-meeting note: The comments were sent to the Sponsor on August 4, 2006).
- The Sponsor agreed to provide narratives (treatment-blinded) of deaths, serious adverse events (SAEs), and discontinuations due to adverse events in ongoing studies using a cut-off date of 8/31/06, for the cUTI/cIAI submission in December, 2006. The 4-month safety update (SU) will contain narratives of deaths, SAEs, and discontinuations due to AEs in the ongoing studies and listings for NP adverse events occurring from 8/31/06 until 12/31/06, in a blinded manner.

**Doripenem Pre-NDA Meeting Questions and Responses.**

**The responses follow the questions and are bolded.**

**8.1 General NDA and eCTD Format Questions**

1. Per FDA's Guidance for Industry "*Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees*" December 2004, Johnson & Johnson Pharmaceutical Research & Development, L.L.C. (J&JPRD) proposes to submit \_\_\_\_\_ for doripenem within a six-month timeframe. Under this scenario, an NDA for cIAI and cUTI would be submitted in December of 2006, \_\_\_\_\_ This would provide an October 2007 PDUFA action goal date for the cIAI/cUTI NDA

\_\_\_\_\_ A visual display of the filing strategy is presented on the following page. We understand that this will require \_\_\_\_\_ *Does the Agency agree with our proposed filing plans for the cIAI/cUTI* \_\_\_\_\_

**The decision regarding a priority review will be made at the time of filing.** \_\_\_\_\_

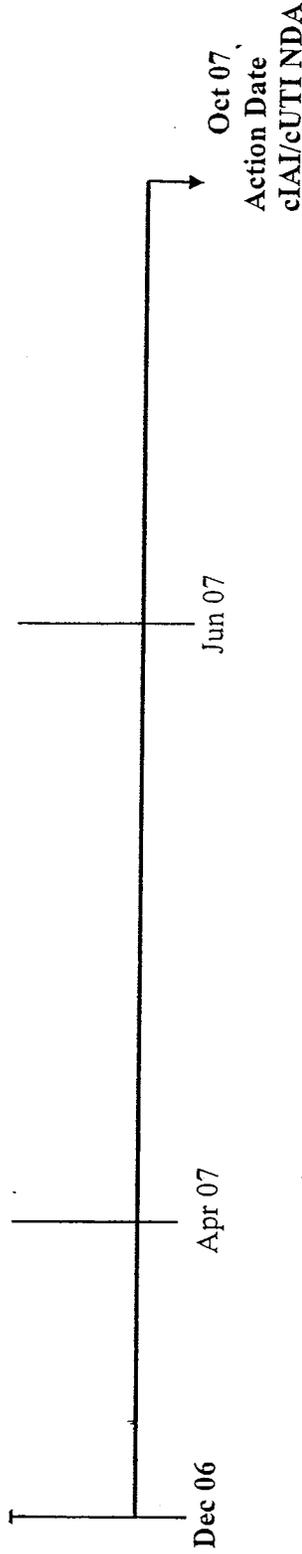
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**APPEARS THIS WAY  
ON ORIGINAL**

**Doripenem NDAs Filing Strategy**

- 2-week Bridging Toxicology Study Report\*    **Amendment to cIAI/cUTI NDA**
- 4-Month Safety Update                            - Target Attainment (%T >MIC) Report
- CMC Stability Update                            - Replace entire micro section of NDA to supplement with NP data
- ADME (DORI-NOS-1007) Study Report       Major sections affected:
- Replace SBPh, SCP and SCS                    in-vitro and in vivo section
- (update with data from ADME study)        Correlations of Provisional Breakpoint Data including susceptibility
- Replace Labeling\*\*
- Replace Labeling\*\*

**cIAI/cUTI**  
test methods  
**NDA**



\* Study report to be submitted as soon as it is available (target date Jan 07) but no later than at the time of the 4-month safety update.  
 \*\* See Section 8.7, Question 1 for a detailed outline of labeling updates.

3. J&JPRD proposes to submit the cIAI/cUTI 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 October 2005). ***Does the Division agree that the proposed content and eCDT format of the cIAI/cUTI NDA \_\_\_\_\_, as outlined in Attachment 1 are acceptable?***

**This is acceptable, however the eCTD Guidance was updated in April 2006. Please see *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* [[HTML](#)] or [[PDF](#)].**

4. The cIAI/cUTI eCTD \_\_\_\_\_ will be built according to, and submitted with, the following dtds/specifications/stylesheets:
- ich-eCTD-3-2.dtd (ICH eCTD Specification v 3.2, 04 Feb 2004 and FDA eCTD Backbone Specification for Modules 2 through 5, 11 Mar 2004)
  - ich-stf-2-0.dtd (FDA eCTD Backbone File Specification for Study Tagging Files, Version 1.1, 09 March 2004)
  - us-regional-v2-01.dtd (FDA eCTD Backbone Files Specification for Module 1, Version 2.01, 01 March 2004)
  - eCTD-1-0.xsl
  - ich-stf-stylesheet.xsl (version 2-0)
  - us-regional-xsl (version 1-0)

***Are the proposed dtds/specifications/stylesheets acceptable?***

**Please note newer versions of specifications below:**

**ich-stf-2-2.dtd (replaces 2-0)**

**ich-stf-stylesheet.xls version 2-2 (replaces 2-0)**

5. All study reports will be submitted as single PDFs using the "legacy-study-report" file-tag value. ***Does the Agency agree with this proposal for submitting study reports and tagging files?***

**This is acceptable**

6. For the STF category element "duration", J&JPRD is defining short/medium/long studies for nonclinical studies as follows: <2 week studies = "short"; 1 & 3 month studies = "medium"; 6 & 9 month studies = "long." *Does the Agency agree with this proposal on the definition of the element "duration" in the STF?*

**This is acceptable**

7. The currently available toolsets used to create SAS transport files may create filenames that contain underscore and capital letter characters. *Is this proposal on naming of the SAS transport files acceptable to the Agency?*

**This is acceptable**

**Please note: J&JPRD did indicate some levels of granularity in the proposed eCTD outline that do not exist within the eCTD specification. Finer granularity may be achieved by adding leaf elements with descriptive names at the *same* level. Please be aware that node extensions may not be used to extend granularity. Feel free to address any further questions to [esub@cdcr.fda.gov](mailto:esub@cdcr.fda.gov).**

## 8.2 CMC Questions

1



**Yes, the Agency is in agreement with this proposal.**

2. Doripenem for Injection is packaged using components known to have a very low extractables profile. As doripenem is a dry powder fill formulation, exposure of the product to the — stopper and glass vial is limited. It is proposed that the safety of the doripenem primary package be supported by including USP <87>, <381> and <661> compendia test results. A supportive discussion can be found in Section 14.1.2.3. *Does the Agency agree with this approach?*

**Yes, the Agency agrees with this approach. LOA's should be provided to reference the DMFs of the components of the primary packaging.**

3. J&JPRD proposes that a package change protocol be included in the cIAI/cUTI NDA that will expedite any necessary post-approval changes to the — and/or bag supplier for storage of the — drug substance. A supportive discussion can be found in Section 14.1.1.4. *Does the Agency agree with the concept of such an — bag change protocol?*

**Yes, the Agency encourages the submission of comparability protocols for post-approval changes in CMC through the use of guidance recommendations. Although still in draft**

form the Guidance for Industry, Comparability Protocols-CMC Information may be referenced. The basic elements included the background document are acceptable.

4. J&JPRD plans to present 12 months' primary drug product stability data in the cIAI/cUTI NDA for three lots of doripenem vials manufactured at the proposed commercial facility and stored in the commercial vial/stopper under ICH conditions. The Company anticipates that we would provide additional — stability data within 7 months of the cIAI/cUTI NDA submission. A supportive discussion can be found in Section 14.1.2.4. *Does the Agency concur with the proposal to supplement the available stability data during review of the cIAI/cUTI NDA?*

Yes, the Agency concurs with the proposal to amend the stability data in the cIAI/cUTI NDA within seven months of submission.

5. *Does the Agency agree with the proposal not to include a specific test for stereoisomeric purity of the doripenem drug substance?* A supportive discussion can be found in Section 14.1.1.6.1.

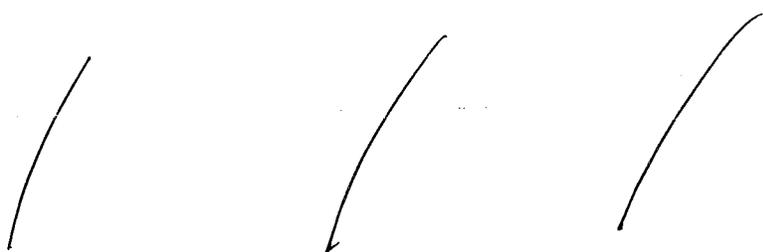
The sponsor has indicated that no potential stereoisomers have been observed with the — starting material and only low levels of the — have been observed / — The proposal not to include routine testing for the drug substance and starting materials will be considered at time of review of the NDA submission along with the assay procedures. The sponsor should ensure that adequate information is included in the Characterization and Control of Drug Substance section of Module 3 of CTD NDA format. The complete impurity profiles of individual batches should also be available.

6. The original doripenem batch records are in Japanese since they were prepared by Shionogi & Co., Ltd., Japan. J&JPRD proposes to only provide a certified English translation of an executed batch record of one lot of the registration stability batches. In addition, J&JPRD will provide a certified English translation of a blank batch record. *Does the Agency agree this is acceptable?*

Yes.

### 8.3 Nonclinical Questions

1.



Yes

2. *Does the Agency agree that the nonclinical studies listed in Attachment 2 are sufficient to support the filing and potential approval of the cIAI/cUTI NDA — NDA?*

The studies submitted appear to support a NDA filing; whether they support approval is a review issue. It is noted that the bridging study in the dog with toxicokinetics will be submitted.

3. J&JPRD plans to submit the data line listings from animal toxicological studies electronically, as scanned attachments to each study report. Since these reports have been provided by our partner Shionogi and translated from Japanese, transferring the files to SAS transport files may not be feasible. Hyperlinking can be performed from the reports to each listing document, but not to individual animal data. *Does the Agency agree that this is acceptable?*

Yes. Please make sure the scanned copies are legible on a computer screen.

4. J&JPRD does not plan to provide a copy of the actual study protocols for the nonclinical studies to be included in the cIAI/cUTI NDA. The study designs are described in sufficient detail in the methods section of each report. J&JPRD will provide any protocol upon request. *Does the Agency agree that this is acceptable?*

Yes

#### 8.4 Microbiology Questions

1. J&JPRD plans to organize the microbiology section of the cIAI/cUTI NDA — according to the outline of the unpublished draft guideline “*Microbiological Data For Antibacterial Drug Products - Development, Analysis, & Presentation: March 2003*”. *Does the Agency agree that this is acceptable?*

Yes

2. In accordance with the unpublished draft guideline “*Microbiological Data For Antibacterial Drug Products - Development, Analysis, & Presentation: March 2003*”, J&JPRD plans to provide the microbiology summary in Module 2, section 2.7 Clinical Summary, subsection 2.7.2.4 and to provide the nonclinical and clinical study reports used in the construction of the microbiology summary in Module 5, subsection 5.3.5.4 Other Clinical Study Reports. This strategy will be followed for both the cIAI/cUTI NDA — NDA. *Does the Agency agree that this is acceptable?*

Yes

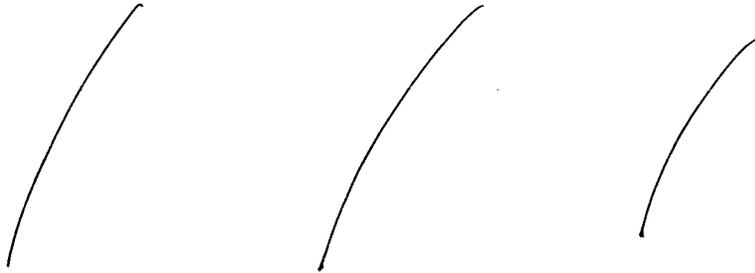
3. There will not be information for doripenem for the category of intracellular antimicrobial concentration assessment, as  $\beta$ -lactams generally do not concentrate intracellularly and thus are considered to be ineffective agents for intracellular pathogens. No specific intracellular concentration data will have been generated for doripenem, although activity against atypical organisms will be assessed. A supportive discussion can be found in Sections 14.3 and 15.3. *Does the Agency agree that intracellular concentrations are not required for filing?*

Yes

4. In the Correlation of Provisional Criteria with Clinical Outcomes sections of the cIAI/cUTI — we propose to establish MIC breakpoints based on analysis of MIC population distributions, clinical and bacteriologic outcomes for target pathogens, and consideration of pharmacokinetics/pharmacodynamics (PK/PD). We will conduct clinical and microbiological outcome analyses by MIC but propose not to conduct similar independent outcome analyses by disk zone diameters. We propose to establish the disk zone breakpoints by correlation with MIC breakpoints based on scattergram analyses. A supportive discussion can be found in Section 15.3. *Does the Agency agree that this is acceptable?*

Yes

5. The Microbiology section of the final label will be consistent with the clinical data obtained in the Phase 3 cIAI, cUTI — studies. Our goal is to achieve a label for doripenem that includes the totality of breakpoint information collected from the cIAI, cUTI — trials. At the time of the cIAI and cUTI filing (December 2006), all the breakpoint data for all relevant organisms will not be available; therefore, we intend to list the susceptible microorganisms within the indication section of the initial cIAI and cUTI label (based on the results of studies in these indications) but will not include specific breakpoint information.



*approach?*

*Does the Agency concur with this*

**The approach to the submission of breakpoints is unacceptable. The Agency strongly recommends that breakpoints be submitted for each organism and for each indication at the time of the submission of the Microbiology data. Separate breakpoints may be necessary for an organism proposed in one indication versus the same organism for another indication. The Agency has seen the need for this after experience with recent NDA submissions. In addition, since each of these indications involves a different anatomical system, the pharmacokinetics of doripenem may vary from one system to another. For example, since doripenem concentrates in the urine, a higher breakpoint may be possible for isolates from cUTI then for isolates from other indications. After submission of separate breakpoints in each indication, it may be that the same organism may have the same breakpoint regardless of indication; however, this determination cannot be made until all of the data is analyzed for each indication independently.**

**8.5 Clinical Pharmacology Questions**

**8.5.1 cIAI/cUTI NDA**

1. As outlined in the 28 February 2006 Type C meeting background document (submitted to IND 64,416 on 27 January 2006, Serial No. 172), J&JPRD plans to evaluate doripenem pharmacokinetics in subjects with end-stage renal impairment, \_\_\_\_\_

Since J&JPRD is still assessing which form(s) of continuous renal replacement therapy will be evaluated, we propose to submit only information from intermittent hemodialysis patients in the cIAI/cUTI NDA. \_\_\_\_\_

*Does the Agency agree?*

**The Agency agrees with submitting information only from patients with end stage renal disease receiving intermittent hemodialysis in the cIAI/cUTI NDA.**

2. At the 28 February 2006 Type C meeting, the Agency agreed that the clinical study report for the human ADME study could be submitted after the initial NDA filing for cIAI/cUTI, but no later than \_\_\_\_\_. Since the Company's filing strategy has changed and we will now be \_\_\_\_\_, J&JPRD proposes to submit the clinical study report for the human ADME study and to update relevant components of the NDA (Module 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Methods, Module 2.7.2, Summary of Clinical Pharmacology Studies, and Module 2.7.4, Summary of Clinical Safety) at the time of the 4-month safety update (4MSU) for the cIAI/cUTI NDA. *Does the Agency agree?*

**The Agency agrees that it is acceptable to submit the final study report for the human ADME study no later than at the time of the 4-month safety update.**

3. Shionogi measured concentrations of doripenem in various body tissues and fluids in several Japanese Phase 2 and Phase 3 studies. The concentrations of doripenem in these tissues and fluids, which are summarized in Section 14.4.6.2, either match or exceed those needed (1-2 µg/mL) to inhibit most target pathogens. Since a 250 mg dose infused over 30 minutes (infusion rate = 8.3 mg/min) was used in most of the Japanese studies assessing tissue and fluid concentrations, these results are considered conservative estimates of expected tissue and fluid concentrations for a Western population where a 500 mg dose infused over 1 hour (infusion rate = 8.3 mg/min) will be used. \_\_\_\_\_

*Does the Agency agree?*

No. \_\_\_\_\_

4. The population pharmacokinetic (PK) model for the cIAI/cUTI NDA will contain data from the Phase 1 studies and the DORI-03 Phase 2 study as outlined in the Population PK

Analysis Plan contained in Attachment 6. *Does the Agency agree with the proposed population PK plan for the cIAI/cUTI NDA?*

**The Agency agrees with the proposed population PK plan for the cIAI/cUTI NDA.**

5. J&JPRD plans to evaluate the target attainment (%T>MIC) data to support the MIC breakpoint determination using the population PK model referenced in Question 4. The report will be filed as an amendment to the cIAI /cUTI NDA \_\_\_\_\_

*Does the Agency concur?*

**Please provide a rationale for submitting the target attainment (%T>MIC) data to support the MIC breakpoint determination at the time \_\_\_\_\_ rather than with the cIAI/cUTI NDA.**

6. J&JPRD previously conducted an exposure-response analysis for cUTI. The results of this analysis indicated no meaningful relationship (please refer to Section 14.4.6.2 of this document as well as the submission filed to IND 64,416 on 23 April 2004; Serial No. 065). Since no additional PK data were obtained from the pivotal Phase 3 cUTI studies, J&JPRD does not plan to perform any additional exposure-response analysis for the cUTI indication nor do we plan to provide any exposure-response reports in the cIAI/cUTI NDA. *Does the Agency agree?*

**The Agency agrees.**

7. In accordance with the FDA guidance for providing regulatory submissions in electronic format, J&JPRD plans to submit electronic PK datasets as study-specific SAS transport files (.xpt) and corresponding data definition files (.pdf files). The datasets will include the following variables for the respective analytes: raw PK sample concentrations, PK sample collection date and time, study drug dosing information, and relevant demographic information. *Is the proposed format acceptable to the Agency?*

**The proposed format is acceptable to the Agency. In addition to sample concentrations, the sponsor should also submit datasets containing individual pharmacokinetic parameters.**

8. Per the eCTD format guidelines, J&JPRD plans to provide the NONMEM datasets in .xpt format and the NONMEM control streams and outputs in .pdf format. *Is the proposed format acceptable to the Agency?*

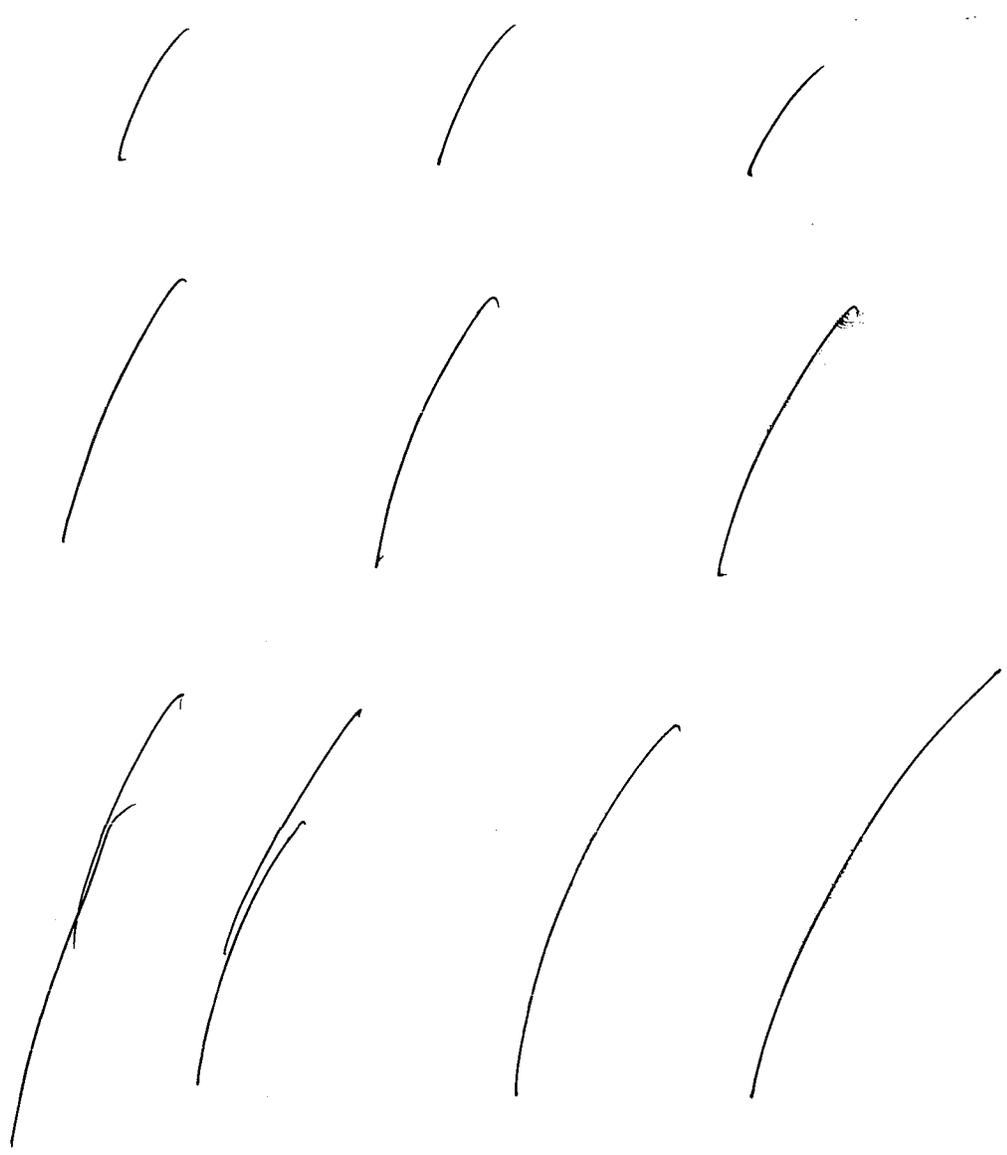
**The Agency agrees that the proposed format is acceptable.**

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_



y.

## 8.6 Clinical and Statistical Questions

### 8.6.1 Content

1. *Does the Agency agree that the clinical pharmacology and Phase 2/3 studies are sufficient to support the filing and potential approval of the cIAI/cUTI NDA* — ?

**Yes, it is adequate for filing. Determination regarding approval will be made during the review.**

2



3. The Company does not plan to provide Appendix 16.2.6 (individual efficacy response data), 16.2.7 (adverse event listings for each subject), 16.2.8 (listing of individual laboratory measurements by subject), and Appendix 16.4 (individual Patient Data Listings) as defined by ICH E3 guideline ("Structure and Content of Clinical Study Reports"). Instead datasets will be provided as part of the case report tabulations. Additional information regarding individual subject data listing is provided in Sections 14.4.7.7.2 and 15.5.4.4.2. *Is this proposal acceptable?*

**The Sponsor should provide Appendices 16.2.6 (individual efficacy response data) and 16.2.7 (adverse event listings for each subject).**

4. The Company proposes not to provide patient profiles since the complete database will be provided in the CRTs. *Does the Agency agree that this is acceptable?*

Yes

5. In accordance with 21 CFR 314.50(f)(2) the Company plans to provide CRFs only for subjects who died or discontinued due to an adverse event and possibly for those subjects outlined in Question #6. *Does the Agency agree this is acceptable?*

**In addition to the CRFs proposed by the Company for submission, the Agency will be requesting a random sample of approximately 10-15% of treatment-blinded CRFs from each pivotal Phase 3 study. In order for the CRFs for this random sample to be included with the initial NDA submission, please provide a dataset that contains unique patient id and treatment group for all patients who were treated as soon as possible so that the random sample can be generated and sent to you.**

6. A subset of subjects enrolled in the Phase 3 UTI studies had urine cultures at test of cure (TOC) or last follow-up visit reported as "contaminated". *Does the Agency believe it is necessary to include the CRFs and source urine culture reports for the above mentioned subjects or are the proposed summary tables adequate?*

**The Agency requests that the CRFs and source urine culture reports for these patients be provided with the NDA.**

7. On 23 May, 2006 J&J submitted an official request to the doripenem IND for a deferral from providing pediatric data until after approval of doripenem use in adults. *Does the Agency agree that this is appropriate and concur to officially grant a deferral (i.e., document via the meeting minutes)?*

**Deferral of pediatric studies is acceptable. However, the proposed pediatric development plan needs further discussion.**

8. For the cIAI/cUTI NDA, J&J plans to submit published literature according to the following proposal:

- All published literature cited in Module 2.5 (Clinical Overview) and in Module 2.7 (Clinical Summaries) in accordance with M4E
- For cIAI/cUTI NDA, J&J will perform a literature search for reports relevant to the clinical safety and effectiveness of doripenem using a cut-off date of 31 August 2006.

For — NDA, relevant literature will be summarized and a report included in Module 5, Section 5.3.5.4, and copies of all relevant references will be provided in Module 5, Section 5.4.

- References cited in clinical study reports will be submitted, but will be available upon request.
  - All references not provided in Module 5 will be immediately available upon request.
- Is the proposal for submission of published literature acceptable to the Agency?*

Yes.

### 8.6.2 Efficacy

9. The Summary of Clinical Efficacy (SCE) for both the cIAI/cUTI NDA — will be prepared in accordance with regulation 21 CFR 314.50(d)(5)(v) calling for an integrated summary of efficacy (ISE) and will be provided in Module 2.7.3. A separate ISE will not be provided in Module 5.3.5.2, Reports of Analyses of Data From More Than One Study. *Is the proposal to submit the SCE in Module 2 and not to submit an ISSE in Module 5 acceptable to the Agency?*

**Yes, the proposal is acceptable. It should be noted however, that the primary efficacy endpoint and determination of efficacy for an indication is based on individual study efficacy results and not on pooled data from multiple studies. Pooled (or integrated) efficacy data may be used to support secondary endpoint determinations, such as microbiological efficacy for a designated micro-organism.**

10. The SCE statistical analysis plans (SAPs) for integration of efficacy data to support indications for cIAI, cUTI, — are included in the pre-NDA briefing document. *Are the proposed SAPs for the SCEs included in the preNDA background document acceptable to the Agency?*

Overall, the SAPs for the SCEs for the cUTI and cIAI seem acceptable. However, additional comments may arise upon review of the revised SAPs for these indications.

11. Within the SCEs for cIAI, cUTI —, the Company plans to conduct subgroup analyses of key efficacy results based on sex, age, race, geographic region, baseline dose adjustment for renal impairment and presence of bacteremia. Indication-specific factors include:

- cUTI: baseline diagnosis
- cIAI APACHE score and site of infection
- 

*Are these subgroup analyses sufficient for the SCE?*

Yes, these subgroup analyses appear to be sufficient for the SCE. Additional analyses may be requested during the course of review based on data submitted. Subgroup analysis by geographic region should include US versus ex-US sites.

### 8.6.3 Safety

12. The Summary of Clinical Safety (SCS) for both cIAI/cUTI — NDAs will be provided in Module 2.7.4 and will contain the level of detail expected for an ISS. Therefore a separate ISS will not be provided in Module 5.3.52, Reports of Analyses of Data From More Than One Study. *Is the proposal to submit the SCS in Module 2 and not to submit an ISS in Module 5 acceptable to the Agency?*

Yes

13. Since doripenem is being evaluated in other indications, safety data collection will be ongoing at the time of cIAI/cUTI NDA. A listing of deaths, SAEs, and discontinuations due to AEs reported in ongoing studies will be provided in SCS using 31 August 2006 cut-off. J&J proposes \_\_\_\_\_

*Is this acceptable?*

**The lists of deaths, SAEs, and discontinuations due to AEs in ongoing studies should be provided as indicated. Narratives for deaths, SAEs and discontinuations due to AEs for all ongoing studies should be submitted to cUTI/cIAI NDA in August 2007 (cut-off date June 2007).**

14. J&J proposes to provide a 4 MSU for cIAI/cUTI wich includes a cumulative listing of deaths, SAEs, and discontinuations due to AEs in those studies that are ongoing at the time of the time of the cIAI/cUTI submission. All events reported after 31 August 2006 until the filing date will be included in the 4MSU. *Does the Agency agree this is acceptable?*

Yes.

15. The SCS in the cIAI/cUTI NDA will include safety data from Phase 2 studies and integrated safety data from Phase 2/3 studies in subjects with cIAI or cUTI. \_\_\_\_\_

\_\_\_\_\_ Details are provided in SCS SAP. *Is the proposed plan for summarization of clinical safety included in the SAPs contained in the background package acceptable?*

**Response to be provided at a later time.**

16. J&J plans to conduct subgroup analysis for TEAEs based on sex, age, race, baseline creatinine clearance status, hepatic impairment status (for cIAI: — only), and geographical region. We also plan to conduct subgroup analyses for concomitant therapies and index infection as detailed in question 17. *Are these subgroup analyses sufficient for the SCS?*

**Yes. Additional analyses may be requested during the review.**

17. In the SCS for the cIAI/cUTI NDA , subgroup analysis for TEAEs will be performed as described in Question 16. In addition, as recommended by ICH CTD guidances, J&JPRD plans to present common AEs and SAEs by selected concomitant medications. Summary tables will be presented for AEs that occurred at  $\geq 1\%$  frequency in subjects being treated with i.v. study drug therapy and the following concomitant medications: (1) vancomycin, (2) aminoglycosides (amikacin, gentamicin, and tobramycin) and (3) sodium valproate. For sodium valproate, J&JPRD will include all neurologically-related AEs, regardless of frequency, as well as all AEs occurring at  $\geq 1\%$  frequency. In addition, since the infection being studied (cUTI, cIAI, ) is the most relevant aspect of the subjects' medical histories, J&JPRD plans to present common AEs and SAEs by indication and not by other components of the subjects' medical histories. Further details can be found in the SAP for SCS contained in Attachment 7.7 of the preNDA briefing document. ***Does the Agency agree that this is acceptable?***

**Yes**

18. The Phase 1 section of the SCS to be included in the cIAI/cUTI NDA will comprise data from the following studies (for subjects with normal renal function only): DORI-01, DORI-02, DORI-04, DORI-NOS-1001, DORI-NOS-1004, DORI-NOS-1005, and DORI-NOS-1006. Data from healthy subjects in the ADME study DORI-NOS-1007 will be integrated in the cIAI/cUTI NDA at the time of the 4MSU. Safety data from subjects with renal impairment in Studies DORI-02 and DORI-NOS-1005 will not be integrated with other studies; but critical results will be discussed in the SCS with reference to the individual study reports. The SCS will include integrated summaries of demographics, exposure information, completion status, and TEAEs. Clinical laboratory test results, ECGs, and vital sign data will not be integrated; critical results will be discussed in the SCS with reference to the individual study reports. Further details can be found in the SAP for SCS contained in Attachment 7.7 of the preNDA briefing document. ***Does the Agency concur?***

**Yes**

19. For the Shionogi clinical pharmacology studies specified as being primary studies to support the NDA (i.e., probenecid drug interaction study, five PK studies in healthy subjects, and the Phase 2 and Phase 3 studies in which tissue and fluid concentration measurements were made), the Company does not plan to integrate the safety data from these studies in the NDA. However, an English translation of the clinical study report with certification will be provided for each study, as agreed upon at the 28 February 2006 Type C meeting. Additional information regarding these studies is provided in Section 14.4.6.2. ***Does the Agency agree that safety data from the Shionogi studies do not need to be integrated in the SCS?***

**Yes**

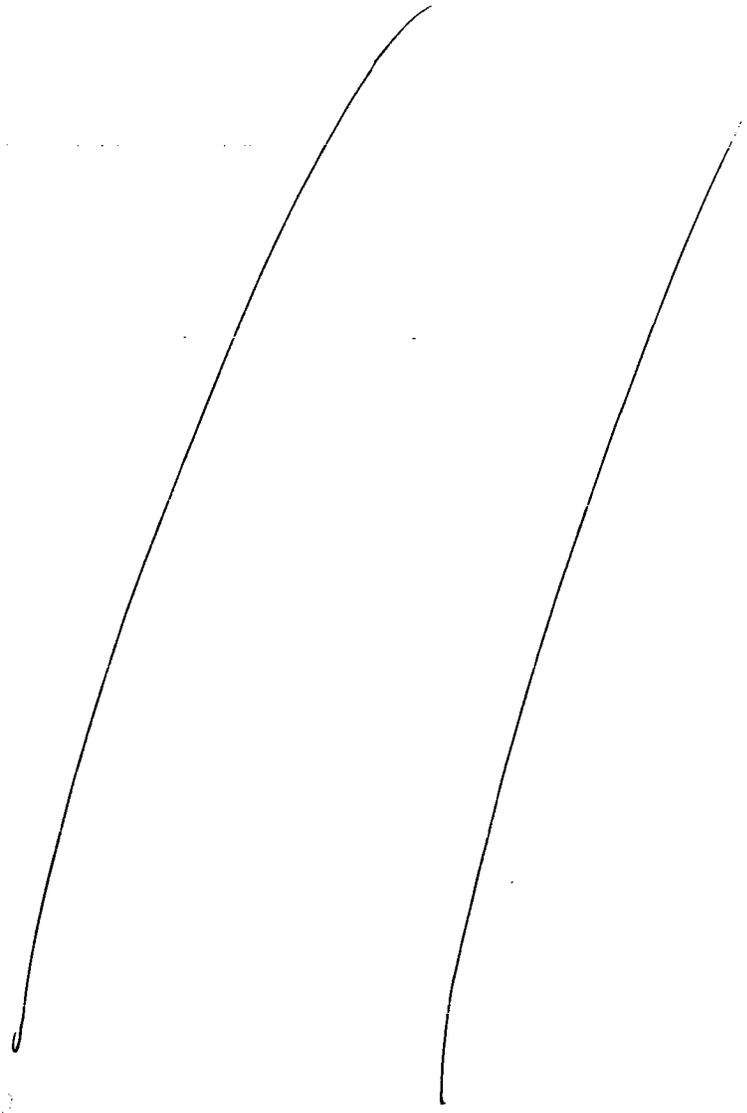
20. In accordance with ICH E3 guidance, narratives describing each death and SAE will be provided in the individual clinical study reports. Premature discontinuations due to AEs will be provided in a listing only and not in narrative format. ***Does the Agency agree with this proposal?***



details regarding benefit-risk management are provided in Section 14.6.2. *Does the Agency agree with the proposed strategy?*

Yes

### 8.7 Labeling



1   Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

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/s/

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Susmita Samanta  
8/25/2006 12:29:19 PM  
Signing for Frances LeSane

Sumathi Nambiar  
8/25/2006 10:23:09 PM



NDA 22-106

INFORMATION REQUEST LETTER

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.  
Attention: Catherine Glamkowski  
Associate Director, North American Regulatory Liaison  
920 U.S. Highway 202  
P.O. Box 300  
Raritan, NJ 08869-0602

Dear Ms. Glamkowski:

Please refer to your December 12, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Doripenem for Injection.

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.

- Provide validation of the ability of the \_\_\_\_\_
- The following statement is found in Section 2.3 of Module 3.2.P.3.5 concerning \_\_\_\_\_  
| | | | |
- The gauge of the needle used to withdraw the suspension during constitution (21-gauge) should be included in the constitution direction in the package insert to ensure a complete suspension transfer.

If you have any questions, call Susmita Samanta, Regulatory Project Manager, at 301-796-1400.

Sincerely,

*{See appended electronic signature page}*

Frances V. LeSane  
Chief, Project Management Staff  
Division of Anti-Infective and Ophthalmology  
Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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/s/

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Frances LeSane  
7/23/2007 01:57:14 PM



NDA 22-106

INFORMATION REQUEST LETTER

Johnson&Johnson Pharmaceutical Research & Development, L.L.C.  
Attention: Catherine Glamkowski  
Associate Director, North American Regulatory Liaison  
920 U.S. Highway 202  
P.O. Box 300  
Raritan, NJ 08869-0602

Dear Ms. Glamkowski:

Please refer to your December 12, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Doripenem for Injection.

We have reviewed your proposed labeling and have identified the following issues and/or deficiencies:

**Highlights**

- Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format.
  - After Initial US Approval, delete the hyphen and replace with a colon
  - Insert one line of white space between each major heading in Highlights
  - Remove italics from the Highlights (except [www.fda.gov/medwatch](http://www.fda.gov/medwatch))
  - Delete the period after **See 17 for PATIENT COUNSELING INFORMATION**
  - For a new NDA, BLA, or supplement, the revision date should be left blank (e.g., Revised: m/yyyy) at the time of submission and will be edited to the month/year of application or supplement approval.
- The drug name must be followed by the drug's dosage form and route of administration. [See 21 CFR 201.57(a)(2)]. Please revise to:  
Tradename (doripenem) injection for intravenous use

**Full Prescribing Information: Contents**

- A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]

**Full Prescribing Information**

- The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [*see Clinical Pharmacology (12.3)*] not [*See Pharmacokinetics (12.3)*]. Please correct the cross-references throughout the labeling. [See PLR Implementation Guidance]
- The Dosage and Administration section does not include all of the storage information for the

- drug (e.g, storage before reconstitution).
- Please change 6.2 Adverse Drug Reaction Information from Spontaneous Reports to 6.2 Postmarketing Experience in the FPI and FPI: Contents
    - Under 6.2, add the statement regarding data from postmarketing spontaneous reports recommended in the Adverse Reactions Labeling Guidance, pages 7 and 8.
  - Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]
  - The “RX only” at the end of the label should be deleted.

Please address the identified deficiencies/issues and re-submit labeling by May 18, 2007. This updated version of labeling will be used for further labeling discussions.

If you have any questions, call Susmita Samanta, Regulatory Project Manager, at 301-796-1400.

Sincerely,

*{See appended electronic signature page}*

Frances V. LeSane  
Chief, Project Management Staff  
Division of Anti-Infective and Ophthalmology  
Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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/s/

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Frances LeSane

5/2/2007 12:48:55 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

**FILING COMMUNICATION**

NDA 22-106

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.  
Attention: Catherine M. Glamkowski  
Associate Director, North American Regulatory Liaison  
920 U.S. Highway 202, P.O. Box 300  
Raritan, NJ 08869-0602

Dear Ms. Glamkowski:

Please refer to your December 12, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Doripenem for Injection.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on February 9, 2007 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issue:

Your justification for the use of a 10% non-inferiority margin in the Phase 3 complicated urinary tract infection studies and a 15% non-inferiority margin in the Phase 3 complicated intra-abdominal infection studies as requested by the Agency on January 26, 2007 has not yet been received. This information is critical in interpreting the results of your studies. Agency review of the adequacy of the justification will be determined after receipt of your submission.

We are providing the above comment to give you preliminary notice of potential review issue. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

If you have any questions, call Susmita Samanta, Regulatory Project Manager, at 301-796-1400.

Sincerely,

*{See appended electronic signature page}*

Frances V. LeSane  
Chief, Project Management Staff  
Division of Anti-Infective and Ophthalmology  
Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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Frances LeSane  
2/22/2007 03:23:26 PM

**MEMORANDUM**

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

**DATE:** January 26, 2007

**TO:** Catherine Glamkowski  
Associate Director, North American Regulatory Liaison  
Johnson & Johnson Pharmaceutical Research & Development

**FROM:** Susmita Samanta  
Regulatory Project Manager  
Division of Anti-Infective and Ophthalmologic Products

**SUBJECT:** Justification for the Non-inferiority Margin  
IND 64,416, Doripenem for Injection

The Division requests that you provide justification for the use of a 10% non-inferiority margin in the Phase 3 complicated urinary tract infection studies and a 15% non-inferiority margin in the Phase 3 complicated intra-abdominal infection studies. Please refer to the Division's comments for your submission dated November 30, 2005, serial number 151. Citing use of the non-inferiority margin in prior approvals is not sufficient. The justification should include the rationale used to estimate the benefit of active drug treatment versus placebo. The non-inferiority margin chosen should preserve at least 50% of this benefit, while controlling for variability. The strategy used to search the literature and pertinent references should be submitted to the NDA.

For the cIAI studies, please provide the reference for your statement that there is a low expectation of cure on placebo for patients with cIAI. This information may be useful in the estimation of the treatment effect of the active control discussed above.

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/s/

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Susmita Samanta  
1/26/2007 02:14:41 PM  
CSO

Sumathi Nambiar  
1/26/2007 02:42:08 PM  
MEDICAL OFFICER



NDA 22-106

**NDA ACKNOWLEDGMENT**

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.  
Attention: Catherine M. Glamkowski  
Associate Director, North American Regulatory Liaison  
920 U.S. Highway 202, P.O. Box 300  
Raritan, NJ 08869-0602

Dear Ms. Glamkowski:

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

Name of Drug Product: Doripenem for Injection

Review Priority Classification: Standard (S)

Date of Application: December 12, 2006

Date of Receipt: December 13, 2006

Our Reference Number: NDA 22-106

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 February 9, 2007, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 12, 2007.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We reference the deferral granted on July 27, 2006, for the pediatric study requirement for this application.

NDA 22-106

Page 2

Please cite the NDA number listed above 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 Anti-Infective and Ophthalmology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If you have any questions, call Susmita Samanta, Regulatory Project Manager, at 301-796-1400.

Sincerely,

*{See appended electronic signature page}*

Frances V. LeSane  
Chief, Project Management Staff  
Division of Anti-Infective and Ophthalmology  
Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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/s/

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Frances LeSane  
1/24/2007 12:33:43 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

**PRESCRIPTION DRUG  
USER FEE COVER  
SHEET**

Form Approved: OMB No. 0910-0297  
Expiration Date: December 31, 2006.

**See Instructions on Reverse Side Before Completing This Form**

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdual/default.htm>

1. APPLICANT'S NAME AND ADDRESS Johnson & Johnson Pharmaceutical Research & Development, L.L.C.  Catherine Giamkowski 920 U.S. Highway 202 P.O. Box 300 Raritan, NJ 08869-0602 United States		4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER N022106	
2. TELEPHONE NUMBER (Include Area Code)  ( 908 ) 704-5360		5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.  IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:  _____ (APPLICATION NO. CONTAINING THE DATA)	
3. PRODUCT NAME TRADENAME (Dotipenem for Injection)		6. USER FEE I.D. NUMBER PD3006841	
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.  <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)  <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)  <input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)  <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)			
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?  <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO (See item 8, reverse side if answered YES)			
Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:  Department of Health and Human Services      Food and Drug Administration      An agency may not conduct or sponsor, and a person is not Food and Drug Administration      CDER, HFD-94      required to respond to, a collection of information unless it CBER, HFM-99      and 12420 Parklawn Drive, Room 3046      displays a currently valid OMB control number. 1401 Rockville Pike      Rockville, MD 20852 Rockville, MD 20852-1448			
SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE <i>Catherine M. Giamkowski</i>		TITLE Associate Director, Regulatory Affairs	DATE 2 Nov 2006



Clinical Pharmacology:

Question #5

This is acceptable as stated.

Question #3

The Agency still recommends that you submit tissue penetration data and proposed label statements with the cIAI/cUTI NDA independent of its relevance to the two indications. Internal discussions regarding the acceptability of the data will occur during the review.

**APPEARS THIS WAY  
ON ORIGINAL**

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/s/

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Susmita Samanta  
10/12/2006 02:51:50 PM  
CSO

Thank you

Sumathi Nambiar  
10/12/2006 02:57:24 PM  
MEDICAL OFFICER

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Deliberative Process

## MEMORANDUM OF TELECON

**MEETING DATE:** July 7, 2004  
**TIME:** 12:00-1:00 P.M.  
**APPLICATION:** 64,416  
**DRUG NAME:** Doripenem for Injection

**FDA Participants:**  
**(Division of Anti-Infective Drug Products)**

James Vidra, PhD, Chemistry Team Leader  
Milton Sloan, PhD, Chemistry Reviewer  
Susmita Samanta, MD, Project Manager

**Peninsula Participants:**

Sharon Powell, PhD, Manager, Regulatory Affairs, PPI  
Debra Odink, PhD, Vice President, Pharmaceutical Chemistry and Product Development

**SUBJECT:**

To discuss if the design of the stability studies described in the briefing package is sufficient to support a change in the rubber stopper.

**BACKGROUND:**

On June 21, 2004, Peninsula Pharmaceutical requested a type A, Chemistry, Manufacturing and Controls meeting. The meeting was granted and scheduled to occur on July 7, 2004. Peninsula sent the meeting package along with the meeting request on June 21, 2004.

**DISCUSSION POINTS:**

After the introduction of the attendees, the Sponsor stated that the Primary stability studies to support NDA filing for doripenem were initiated about a month and a half ago, using the stopper. Recently, the Sponsor has become aware of a formulation change of the stopper which involved removal of a component — The Sponsor now proposes to include the stopper formulation change in the site specific stability batch. These studies would result in 12 months long-term data on 3 batches using the — stopper and 3 months long term data on one site specific batch using the new stopper. The Sponsor wanted to have FDA agreement and feedback on the new proposed stability plan to support the stopper formulation change. There are two issues that the Sponsor wanted FDA's input on:

1. It is the Sponsor's understanding that the \_\_\_\_\_  
\_\_\_\_\_ The current stability plan includes storage in the upright position only. Is this acceptable?

2. Will the data available at time of filing from the site specific batch using the new stopper be sufficient to support our NDA submission?

The Division stated that:

- No problem with amount of data the Sponsor will have available at the time of submission.
- 

The Sponsor responded that the target product label for preparation of this product require that the vial be reconstituted and then transferred to the IV bag. Since the product is not intended for intramuscular use, there is no need to hold the reconstituted drug in the vial. Therefore, the Sponsor will be conducting stability studies in the IV bags to support the use period. The site specific batch is under both long term and accelerated stability.

The Division asked the Sponsor about another issue the Sponsor mentioned before, that the 500 mg vial is not being completely dissolved. The Sponsor responded that their strategy is to address the solubility limitation in the vial with product label instructions. There will be instructions in the label to transfer the diluent to the vial and shake the vial. The suspended material will be transferred to a bag,

The Division asked if that will result in totally dissolved product.

The Sponsor said yes. The solution resulting after the transfer to the bag is approximately 5 mg/ml, far enough below the limit that there are no issues of undissolved particles. The solubility limit of doripenem is  $\sim$ ng/ml.

There were no unresolved issues and the telecon ended.

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Jim Vidra  
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## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** May 3, 2004  
**TIME:** 11:30-1:00 P.M.  
**LOCATION:** Corporate Building  
**APPLICATION:** 64,416  
**DRUG NAME:** Doripenem for Injection

**TYPE OF MEETING:** End of Phase 2

**MEETING CHAIR:** Janice Soreth, M.D.

**MEETING RECORDER:** Susmita Samanta

### FDA ATTENDEES:

#### Division of Anti-Infective Drug Products (HFD-520)

Janice Soreth, MD, Division Director  
Jean Mulinde, MD, Clinical Team Leader  
Susan Thompson, MD, Clinical Reviewer  
Amy C. Nostrandt, DVM, PhD, Pharmacology/Toxicology Reviewer  
Connie Mahon, MS, Acting Microbiology Team Leader  
Peter Coderre, PhD, Microbiology Reviewer  
Bob Osterberg, PhD, Pharmacology/Toxicology Team Leader  
Daphne Lin, PhD, Statistical Team Leader  
Thamban Valappil, PhD, Statistical Reviewer  
Sue Bell, PhD, Statistical Reviewer  
Venkat Jarugula, PhD, Clinical Pharmacology and Biopharmaceutics, Team Leader  
(DPE III)  
Chuck Bonapace, PhD, Clinical Pharmacology and Biopharmaceutics, Senior Reviewer (DPE III)  
Arzu Selen, PhD, Clinical Pharmacology and Biopharmaceutics, Deputy Division Director (DPE III)  
Don Stanski, MD, Scientific Advisor to the CDER Director  
Sumati Nambiar, MD, Acting Clinical Team Leader  
Ed Cox, MD, Acting Office Director for ODE IV  
Jenny Zheng, PhD, Biopharmaceutical Reviewer  
John Powers, MD, Lead Medical Officer for Antimicrobial Development, ODE IV  
Frances Lesane, Chief, Project Management Staff  
Susmita Samanta, MD, Project Manager

### PENINSULA PHARMACEUTICALS ATTENDEES:

Matthew A. Wikler, MD, MBA, FIDSA	CMO & Executive V.P., PPI
Ian Friedland, MD	Sr. Director, Clinical Development, PPI
Rebecca Redman, MD	Sr. Director, Clinical Development, PPI
James Ge, MD, PhD	Sr. Director, Pre-Clinical Development, PPI
Georgina Kilfoil, MBA	V.P., Alliances & Project Management, PPI
Ursula Fritsch, PharmD	Sr. Director, Global Regulatory Affairs, PPI

Sharon Powell, PhD  
Lily Llorens Mantelle, PhD  
Takuko Yamada Sawada

Manager, Regulatory Affairs, PPI  
Director of Biometrics, PPI  
General Manager, Strategic Development  
Shionogi & CO., LTD.

## BACKGROUND

On February 18, 2004, Peninsula Pharmaceutical requested an end-of-phase 2 meeting. The meeting was granted and scheduled to occur on May 3, 2004. Peninsula sent the meeting package on April 6, 2004.

## MEETING OBJECTIVE:

The main objective of the meeting was to gain concurrence on the design of the phase 3 trials.

## DISCUSSION POINTS:

After the introduction of the attendees, the Sponsor briefly presented key aspects of their phase 3 program. In the briefing package, the Sponsor included several questions for the Division. Responses to those questions and comments on protocols were sent to the Sponsor before the meeting and are repeated here for better understanding of the discussion.

### Nonclinical:

1. Are the data from the nonclinical study reports submitted to date as well as the plans for additional nonclinical studies outlined in this package sufficient to support the Phase 3 studies and the NDA filing?

At this time, there does not appear to be a need for additional nonclinical pharmacology or toxicology studies.

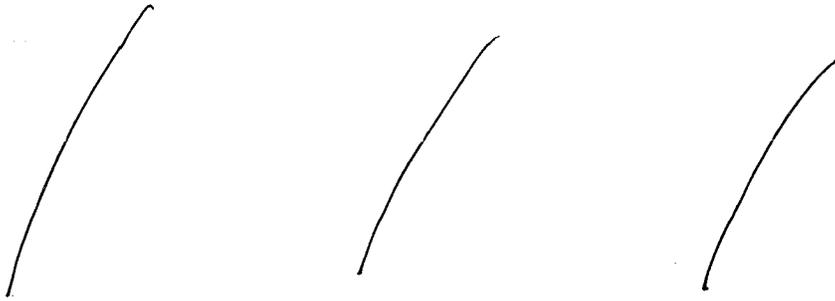
The Division previously recommended that all MIC data be current; for New Molecular Entities (NMEs), the data should be current to within the last three years prior to the submission of the NDA. As long as these data are provided along with provisional breakpoints, the Sponsor should be able to proceed to Phase 3 studies.

2. Is it acceptable to submit the final breakpoint package at the time of the NDA filing?

Yes. However, the Sponsor must submit data in support of the provisional interpretive criteria prior to initiation of phase 3 clinical trials. These data are derived from both the *in vitro* and *in vivo*

preclinical efficacy studies. Final breakpoints will be determined at the end of the NDA review by the Microbiology Reviewer.

3.



Clinical:

1. Are the numbers of patients projected to be exposed to doripenem adequate for establishment of the safety database for the NDA filing?

Yes, provided no unexpected safety signals present that require further exploration.

2. Are the numbers of patients exposed to prolonged (4 h) infusion adequate to establish the safety of this dosing regimen?

Yes

3. Are the proposed phase 3 studies as designed adequate to support approval of doripenem for the intended indications?

Complicated UTI (cUTI) - Yes. Complicated intraabdominal infections (cIAI) study designs will be discussed at the End of Phase 2 meeting. The description of the meeting discussion starts on page 7.

4. For the proposed phase 3 studies, does the FDA agree with a) The definitions of clinical and microbiological outcome? b) The proposed dosing regimens? c) The allowed adjunctive therapy for each protocol? d) The choice of anti-microbials for switch to oral therapy? e) The allowed adjunctive therapy for each protocol? e) The choice of anti-microbials for switch to oral therapy?

cUTI - Yes. cIAI study designs will be discussed at the EOP2 meeting.

5. As most of these studies allow for switch to oral therapy, does the FDA feel that the proposed timing and evaluation criteria for switch to oral therapy, and minimal length of parenteral therapy with study drug, will allow for the evaluation of the efficacy of doripenem?

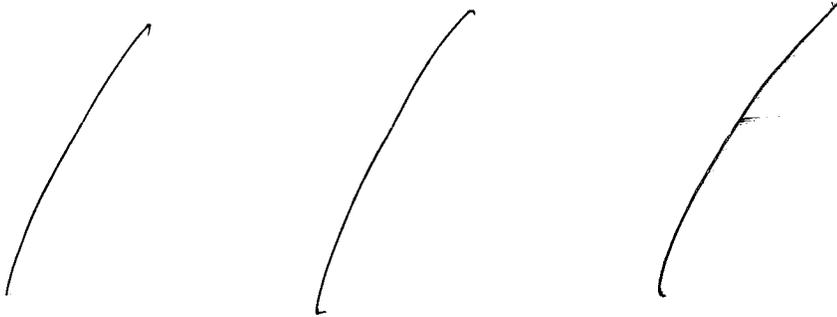
We agree that the proposed timing and evaluation criteria for switch to oral therapy and minimal length of parenteral therapy with study drug will allow for the evaluation of doripenem's efficacy. However, it is important to note that sufficient patients must receive the greatest proposed duration

of therapy for each indication in order to provide safety data to support labeling for the requested duration of use.

6.

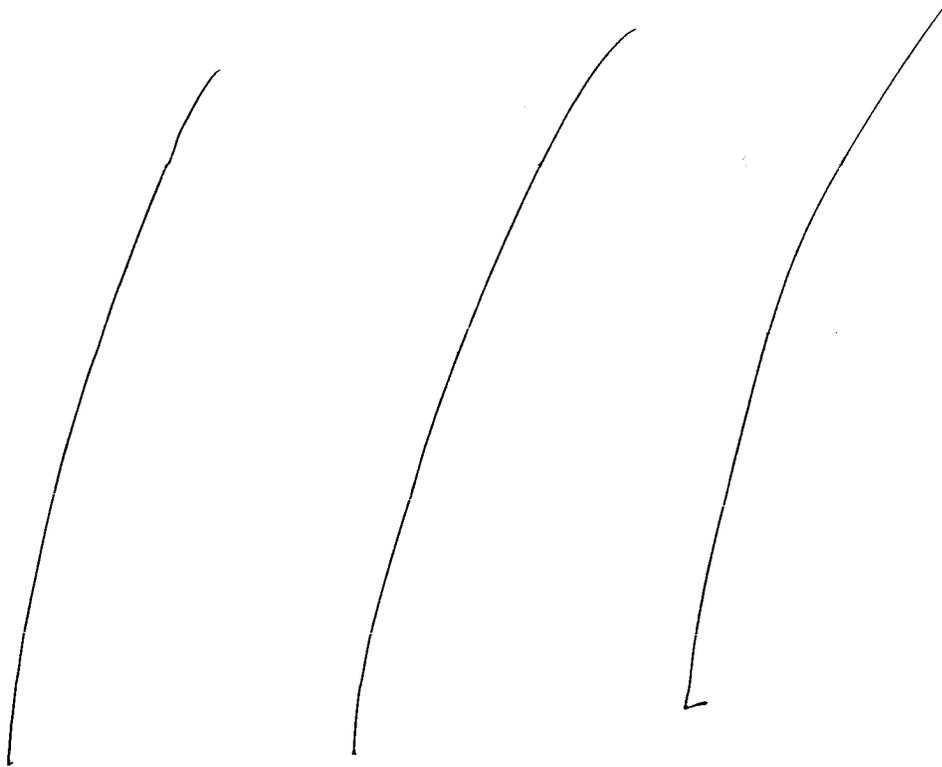


7.



Miscellaneous

1. We note Peninsula's plans to conduct a Phase I study to describe doripenem's effect on the QTc. We strongly urge the sponsor to submit the protocol to the DAIDP for review prior to initiation of this study to ensure that we reach consensus on the most appropriate study design.

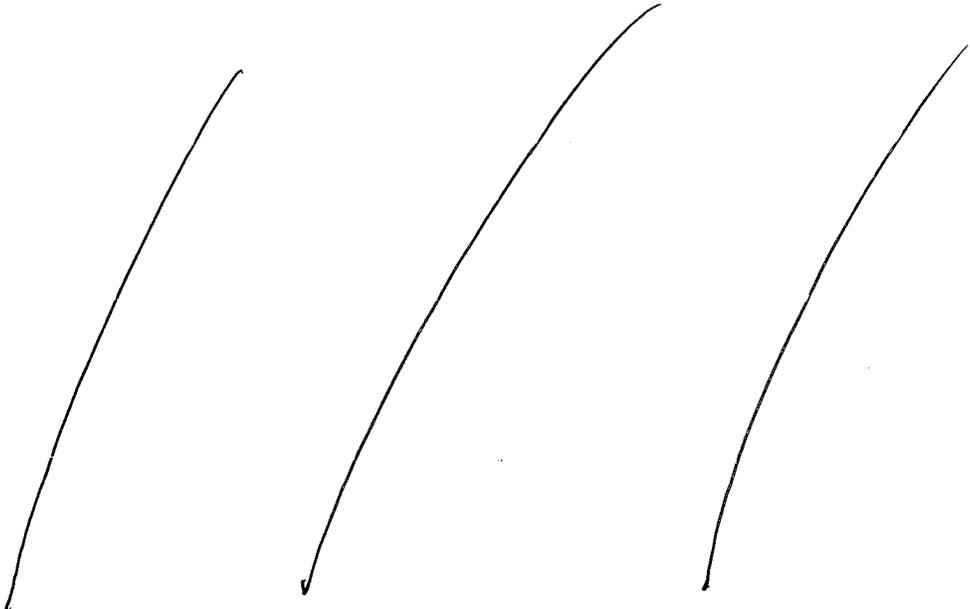


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- The Sponsor has reviewed the Division's recommendations regarding delta, 10% for the cIAI \_\_\_\_\_ trial. The selection of delta is still under consideration and in future, the Sponsor will discuss this issue with the Division further.

The following issues were discussed from a clinical pharmacology point:

- The Sponsor agreed to enroll patients with severe renal impairment ( $CL_{CR} < 30$  mL/min) in addition to mild and moderate renal impairment in studies DORI-07, DORI-08, \_\_\_\_\_
- For patients with moderate renal impairment, the Sponsor agreed to change the doripenem dosage regimen from 500 mg q12h to 250 mg q8h for all Phase 3 studies. The doripenem dosage regimen for patients with severe renal impairment will remain 250 mg q12h.
- The Division asked the Sponsor to consider collecting sparse samples for Phase 3 studies \_\_\_\_\_ the Sponsor stated that they are planning to collect samples from the intra-abdominal infection trials (DORI-07 and DORI-08) \_\_\_\_\_, but not for complicated urinary tract infection trials (DORI-05 and DORI-06). The Division stated that this was acceptable.
- The sponsor agreed to alter the dosage adjustment of meropenem for patients with renal impairment in studies DORI-07 and DORI-08 based on the meropenem approved labeling.
- The Division asked the Sponsor if any simulations were performed to predict the outcomes of phase 3 trials (microbiological/clinical) based on the pharmacokinetic/pharmacodynamic relationships for doripenem. The Sponsor stated that they have not considered it and felt that there was not sufficient clinical data to perform simulations at this time.

The following statistical issues were discussed:

- The Sponsor estimated that for complicated intra-abdominal studies, the response rate will be 80% and the evaluability rate will be 65%. Based on these assumptions, the proposed study would have a 80% power to demonstrate noninferiority with a two-sided alpha of 0.05 and a delta of 0.15. The Division pointed out that if the assumptions used by the Sponsor are even minimally incorrect, then studies may not even meet the efficacy criteria proposed by the Sponsor.
- The Sponsor inquired as to whether or not the Division would find it acceptable to pre-specify criteria that allowed an increase in sample size if the evaluability rates were not as predicted. The Division stated that they would consider this option, but requested that the Sponsor submit the proposal for review.

The following microbiologic issues were discussed:



**DECISIONS (AGREEMENTS) REACHED:**

- The Sponsor will amend the protocols as agreed and submit a proposal for interim analysis.
- The Sponsor will submit a detailed proposal that describes rules that would be followed for sample size re-estimation.
- The Sponsor will further consider the issue of appropriate delta for the cIAI trials, and will have further discussions with the Division on these issues.

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Janice Soreth  
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Frances LeSane  
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