

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204016Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 204016

SUPPL #

HFD #

Trade Name

Generic Name Zoledronic Acid Injection

Applicant Name Hospira, Inc.

Approval Date, If Known

### 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)(2)

b) 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:

c) Did the applicant request exclusivity?

YES  NO

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

d) 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# 021223

NDA#

NDA#

2. Combination product.

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

YES  NO

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

NDA#

NDA#

NDA#

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

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

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

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

answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

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

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

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

YES  NO

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

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

YES  NO

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

YES  NO

If yes, explain:

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

YES  NO

If yes, explain:

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

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

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

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

Investigation #1 YES  NO

Investigation #2 YES  NO

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

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

Investigation #1 YES  NO

Investigation #2 YES  NO



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

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

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

YES  NO

If yes, explain:

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Name of person completing form: Jeannette O'Donnell  
Title: Regulatory Project Manager  
Date: 12/15/15

Name of Office/Division Director signing form: Geoffrey Kim, MD  
Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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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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JEANNETTE L O'DONNELL  
12/28/2015

GEOFFREY S KIM  
12/28/2015

edr  
NDA 204016  
LD=  
SP=  
11/30/2012  
Hospira

### Debarment Certification

Zoledronic Acid Injection

Section 306(k) of the Federal Food, Drug and Cosmetic Act (the Act) (21 U.S.C. 335a(k)):

"Any application for approval of a drug product shall include

- (1) a certification that the applicant did not and will not use in any capacity the services of any person debarred under subsection (a) or (b) in connection with such application, and

**Hospira, Inc. hereby certifies that it did not and will not use, in any capacity, the services of any person debarred under section 306 of the Act in connection with this application.**

**Hospira, Inc. hereby states that it has no such convictions to list.**

Lisa Zboril

Lisa Zboril  
Director, Global Regulatory Affairs  
Hospira, Inc.  
275 North Field Drive  
Dept. 0389, Bldg. H2  
Lake Forest, IL 60045-5046

17 Nov 2011

Date



**1.3.3 Generic Drug Enforcement Act (Debarment) Certification**

As required under Section 306(k)(1) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 335a(k)), a signed certification statement from Hospira, Inc. is provided herein.

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 204016 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Established/Proper Name: Zoledronic Acid Solution Dosage Form: Intravenous Infusion		Applicant: Hospira, Inc. Agent for Applicant (if applicable):
RPM: Jeannette O'Donnell		Division: Oncology Products 1
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><b>For ALL 505(b)(2) applications, two months prior to EVERY action:</b></p> <ul style="list-style-type: none"> <li>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</li> <li>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul> <p><input checked="" type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>)            Date of check: 12/7/15</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>1/2/16</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input type="checkbox"/> None CR: 11/29/12 TA: 7/3/13
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority:  Standard  Priority  
 Chemical classification (new NDAs only):  
 (*confirm chemical classification at time of approval*)

- |   |   |
|---|---|
| <input type="checkbox"/> Fast Track                       | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input type="checkbox"/> Rolling Review                   | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input type="checkbox"/> Breakthrough Therapy designation |   |

**(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))**

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)  
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR  
 Submitted in response to a PMC  
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)  
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS:  MedGuide  
 Communication Plan  
 ETASU  
 MedGuide w/o REMS  
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

### Action Letters

❖ Copies of all action letters (including approval letter with final labeling)	Action(s) and date(s) Approval: 12/28/15 Tentative Approval: 7/3/13 CR: 11/29/12
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### Labeling

❖ Package Insert (write submission/communication date at upper right of first page of PI)	
• Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	<input checked="" type="checkbox"/> Included
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
• Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	<input type="checkbox"/> Included
• Original applicant-proposed labeling	<input type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
• Most-recent draft labeling	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
• Acceptability/non-acceptability letter(s) (indicate date(s))	Not Applicable – No proprietary name requested
• Review(s) (indicate date(s))	
❖ Labeling reviews (indicate dates of reviews) RPM 4/10/2012, 7/2/13 Combined RPM and Clinical labeling review: 12/21/15 & 12/22/2015 DMEPA 7/3/13, 10/3/12, 11/15/12 and 11/13/15 Product Quality: 11/13/15	RPM: <input checked="" type="checkbox"/> None DMEPA: <input checked="" type="checkbox"/> None DMPP/PLT (DRISK): <input type="checkbox"/> None OPDP: <input type="checkbox"/> None SEALD: <input type="checkbox"/> None CSS: <input type="checkbox"/> None Product Quality <input checked="" type="checkbox"/> None Other: <input type="checkbox"/> None

### Administrative / Regulatory Documents

❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting (indicate date of each review)	8/23/12
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input type="checkbox"/> Not a (b)(2) 12/8/15
❖ NDAs only: Exclusivity Summary (signed by Division Director)	<input checked="" type="checkbox"/> 12/28/15
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> <li>This application is on the AIP <ul style="list-style-type: none"> <li>If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>Date reviewed by PeRC _____</li> <li>If PeRC review not necessary, explain: <u>505(b)(2) that does not need PeRC</u></li> </ul>	
❖ Breakthrough Therapy Designation	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)</li> </ul>	
<ul style="list-style-type: none"> <li>CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul> <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the <a href="#">MPC SharePoint Site</a></i>)</p>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) ( <i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include previous action letters, as these are located elsewhere in package</i> )	
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> <li>If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> <li>Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg 1/2/2012
<ul style="list-style-type: none"> <li>EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) Teleconferences</li> </ul>	9/10/12, 2/6/13, and 6/3/13
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>Date(s) of Meeting(s)</li> </ul>	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 7/3/13, 11/29/12, 12/28/15
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 7/3/13, 11/15/12
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None
<b>Clinical</b>	
❖ Clinical Reviews	

<ul style="list-style-type: none"> <li>Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> No separate review 11/2/12
<ul style="list-style-type: none"> <li>Clinical review(s) (<i>indicate date for each review</i>)</li> </ul>	11/1/12
<ul style="list-style-type: none"> <li>Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input checked="" type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)</li> </ul>	No Clinical studies performed
<ul style="list-style-type: none"> <li>❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul> </li> </ul>	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)</li> </ul>	<input checked="" type="checkbox"/> None requested
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
<ul style="list-style-type: none"> <li>❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)</li> </ul>	<input type="checkbox"/> No separate review
<ul style="list-style-type: none"> <li>Clinical Microbiology Review(s) (<i>indicate date for each review</i>)</li> </ul>	<input type="checkbox"/> None
<b>Biostatistics</b> <input checked="" type="checkbox"/> None	
<ul style="list-style-type: none"> <li>❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)</li> </ul>	<input type="checkbox"/> No separate review
<ul style="list-style-type: none"> <li>Statistical Team Leader Review(s) (<i>indicate date for each review</i>)</li> </ul>	<input type="checkbox"/> No separate review
<ul style="list-style-type: none"> <li>Statistical Review(s) (<i>indicate date for each review</i>)</li> </ul>	<input type="checkbox"/> None
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
<ul style="list-style-type: none"> <li>❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> <li>Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> No separate review 6/12/13
<ul style="list-style-type: none"> <li>Clinical Pharmacology review(s) (<i>indicate date for each review</i>)</li> </ul>	<input type="checkbox"/> None 10/17/12, 6/14/13
<ul style="list-style-type: none"> <li>❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)</li> </ul>	<input checked="" type="checkbox"/> None requested
<b>Nonclinical</b> <input type="checkbox"/> None	
<ul style="list-style-type: none"> <li>❖ Pharmacology/Toxicology Discipline Reviews</li> </ul>	
<ul style="list-style-type: none"> <li> <ul style="list-style-type: none"> <li>ADP/T Review(s) (<i>indicate date for each review</i>)</li> </ul> </li> </ul>	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> <li> <ul style="list-style-type: none"> <li>Supervisory Review(s) (<i>indicate date for each review</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> No separate review 10/17/12
<ul style="list-style-type: none"> <li> <ul style="list-style-type: none"> <li>Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> None 10/17/12
<ul style="list-style-type: none"> <li>❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> No carc
<ul style="list-style-type: none"> <li>❖ ECAC/CAC report/memo of meeting</li> </ul>	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)</li> </ul>	<input checked="" type="checkbox"/> None requested

<b>Product Quality</b> <input type="checkbox"/> None	
❖ <b>Product Quality Discipline Reviews</b>	
• Tertiary review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 10/11/12
• Secondary review (e.g., Branch Chief) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 11/2/12, 11/15/12
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team <i>Biopharmaceutics</i> <i>Microbiology/Sterility</i>	<input type="checkbox"/> None 9/10/12 10/4/12
❖ <b>Environmental Assessment (check one) (original and supplemental applications)</b>	
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	10/11/12
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ <b>Facilities Review/Inspection</b>	
<input type="checkbox"/> Facilities inspections ( <i>action must be taken prior to the re-evaluation date</i> ) ( <i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i> )	<input checked="" type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul>	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
<ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul>	<input checked="" type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> <li>• Notify the CDER BT Program Manager</li> </ul>	<input type="checkbox"/> Done ( <i>Send email to CDER OND IO</i> )
❖ For products that need to be added to the flush list (generally opioids): <a href="#">Flush List</a> <ul style="list-style-type: none"> <li>• Notify the Division of Online Communications, Office of Communications</li> </ul>	<input type="checkbox"/> Done <b>Not applicable</b>
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done <b>Not applicable</b>
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input type="checkbox"/> Done <b>Not applicable</b>
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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/s/

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JEANNETTE L O'DONNELL  
12/30/2015

**From:** [Stephens, Olen](#)  
**To:** [O'Donnell, Jeannette](#); [Wang, Xing](#); [Chen, Xiao H](#)  
**Subject:** RE: final labels back for NDA 204016  
**Date:** Thursday, December 17, 2015 9:18:28 AM  
**Attachments:** FW (b) (4) please see below.msg

---

I saw one more thing that needs to be addressed. The C/C label states (b) (4). We have very stringent requirements for this claim (please see attached). Xing/Xiao-Hong, let's get together about this later today.

Olen

---

**From:** O'Donnell, Jeannette  
**Sent:** Thursday, December 17, 2015 9:15 AM  
**To:** Wang, Xing; Stephens, Olen; Chen, Xiao H  
**Subject:** final labels back for NDA 204016  
**Importance:** High

Hi All,

As chemistry was the only division to request a change (b) (4) to "single dose," I'm sending these labels to you to make sure you're happy with the changes. If anything else is needed please let me know.

*Thanks,*

*Jeannette O'Donnell*

*Regulatory Project Manager*

*Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products*

*OND/CDER/FDA*

*Phone: 240-402-4978*

*Fax: 301-796-9845*

*Email: [Jeannette.Odonnell@fda.hhs.gov](mailto:Jeannette.Odonnell@fda.hhs.gov)*

**From:** [Srinivasachar, Kasturi](#)  
**To:** [Stephens, Olen](#)  
**Subject:** FW: (b) (4) please see below  
**Date:** Wednesday, August 20, 2014 9:42:10 AM

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**From:** Lostritto, Richard T  
**Sent:** Friday, March 08, 2013 3:33 PM  
**To:** Lostritto, Richard T  
**Subject:** FW: (b) (4) please see below

Folks,

Here is the bottom line on the (b) (4) issue with regards to labeling in ONDQA reviews and advice to sponsors and applicants. First, ONDQA does not recommend to allow (b) (4) in any new labeling. The appropriate corresponding statements which may be proposed and used by the regulated industry are provided in the excerpt from the guidance below.

Please note the last paragraph which indicates that action "should" be taken to correct labels that have non compliant labeling statements (e.g., using the word (b) (4) ) regarding natural rubber latex or variant related terms such as (b) (4) . Please discuss and obtain concurrence from your Branch Chief (and in turn the Division Director) before advising the regulated industry to take corrective action on inappropriate latex labeling statements for approved drug products. This may involve a broader review team as well.

Finally, this guidance does not remove the statutory requirement that products which DO knowingly contain natural rubber latex must indicate so in the labeling

Thank you and have a nice weekend.

Rik.

Currently, there are no regulations requiring a manufacturer to state that natural rubber latex was not used as a material in their medical product or medical product container. If a manufacturer elects to include a statement in medical product labeling indicating that natural rubber latex or synthetic derivatives of natural rubber latex were not used as materials in the manufacture of their medical product and container, FDA recommends the use of the statement **“Not made with natural rubber latex.”** If this statement is made without any qualification, it must apply to the entire product and all of its packaging. For certain medical products, statements regarding “not made with natural rubber latex” may be appropriate only for certain components. In this case a manufacturer may elect to make a statement that the specific component is not made with natural rubber latex. For example, if the particular presentation or part of the presentation (e.g., vial stopper or syringe) is not made with natural rubber latex, FDA recommends the statement **“The <vial stopper> is not made with natural rubber latex.”**

These statements **“Not made with natural rubber latex”** and **“The <vial stopper> is not made with natural rubber latex”** communicate that natural rubber latex was not used as a

material in the finished product or as a material in the container. At the same time, the statement does not make the unsupported claim that the medical product is (b) (4) of or (b) (4) natural rubber latex (i.e., materials or contamination), which may promote a false sense of safety to users who are allergic to natural rubber latex. Finally, use of a consistent scientifically supportable labeling statement will reduce confusion among FDA staff, medical product manufacturers, and medical product users.

Manufacturers who currently include statements such as (b) (4) or (b) (4) in medical product labeling should update their medical product labeling to show the recommended labeling statement “**Not made with natural rubber latex**” or “**The <vial stopper> is not made with natural rubber latex**” as appropriate. Alternatively, manufacturers should consider removing (b) (4) type statements from medical products and medical product packaging. Manufacturers may contact the Center that regulates the medical product for guidance on the appropriate regulatory mechanism to update the labeling.

---

**From:** Lostritto, Richard T

**Sent:** Friday, March 08, 2013 11:55 AM

**To:** Lostritto, Richard T

**Subject:** FW: (b) (4) please see below

FYI.

Rik

---

**From:** Jayan, Geetha C

**Sent:** Friday, March 08, 2013 11:48 AM

**To:** Simmons, Janesia; Watson, Anthony; Bailey, Michael T; Murphey, Sheila A; Ryan, Michael J; Lucas, Anne D.; Millen, Kenneth; Lostritto, Richard T; Bishop III, John; Evans, Cory; O'Lone, Martha; Goldsberry, Diane S.; Mafnas, Neil; Nowalk, Ronald T; Anderson, Hope; Dar, David; Kroehling, George; Slater, Jay; Finn, Theresa; Wolfgang, Edward; Wyatt, Michael (Keith)

**Cc:** Mitchell, Diane A.; Maisel, William

**Subject:** Re: (b) (4) please see below

Hi (b) (4) team:

Great job, Cudos to all of you!

It has been a pleasure working with you all on this. Thank you.

What a great way to start the weekend, Have a wonderful one.

*Geetha*

\*\*\*\*\*

Geetha C. Jayan

Tel: 301-796-6300

e-mail: [geetha.jayan@fda.hhs.gov](mailto:geetha.jayan@fda.hhs.gov)

\*\*\*\*\*

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**From:** Simmons, Janesia

**Sent:** Friday, March 08, 2013 9:54 AM

**To:** Watson, Anthony; Bailey, Michael T; Murphey, Sheila A; Ryan, Michael J; Lucas, Anne D.; Millen, Kenneth; Lostritto, Richard T; Jayan, Geetha C; Bishop III, John; Evans, Cory; O'Lone, Martha; Goldsberry, Diane S.; Mafnas, Neil; Nowalk, Ronald T; Anderson, Hope; Dar, David

**Subject:** FW: CDRH Distribution of Communication Products -- Medical Products that are Not Made with Natural Rubber Latex Draft Guidance -- ACTION: FYI ONLY

FYI-

Thank you for all of your hard work on this issue!

**Janesia Simmons**

**FDA/CDRH/OCE**

**301-796-5854**

---

**From:** Simmons, Janesia

**Sent:** Friday, March 08, 2013 9:50 AM

**To:** Shuren, Jeff; Maisel, William; Stade, Nancy; McMurry-Heath, Michelle; Long, Mary (Peper); CDRH Office Directors; CDRH Deputy Office Directors; Mitchell, Diane A.; Jackler, Karen; CDRH-OCER-DHC-MGRS; Joseph, Stephanie; Clayton-Jeter, Helene; Mallis, Elias; Sutton, William; Tartal, Joseph; Pak, Yung; Benson, Cynthia M.; Alderton, Bonnie J.; Jefferson, Erica; Liscinsky, Morgan; Bolek, Michelle; MedWatch Safety Alerts

**Subject:** CDRH Distribution of Communication Products -- Medical Products that are Not Made with Natural Rubber Latex Draft Guidance -- ACTION: FYI ONLY

**This e-mail is to inform you that the Draft Guidance, FDA Consumer Update, and FDA Press Release for Medical Products that are Not Made with Natural Rubber Latex are "live".**

**Draft Guidance:**

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm340972.htm>

**FDA Consumer Update:**

<http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm342641.htm>

**FDA Press Release:**

<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm342855.htm>

**Talking Points:** (FYI- Talking Points are used by FDA in responding to questions from the public, and

are not published or posted to the web)

<< File: FINAL Key Messages and QA -- Natural Rubber Latex Labeling 3-8-13.doc >>

**Communication Working Group:** Watson, Anthony (ODE); Bailey, Michael T (ODE); Murphey, Sheila A (ODE); Ryan, Michael J (ODE); Lucas, Anne D. (OSEL); Millen, Kenneth (OC); Lostritto, Richard T (CDER); Jayan, Geetha C (OCD); Bishop III, John (CBER); Evans, Cory (CVM); O'Lone, Martha (CBER); Goldsberry, Diane S. (OC); Mafnas, Neil (OC); Nowalk, Ronald T (OC); Anderson, Hope (CBER); Jackler, Karen (OCD); Long, Mary (Peper) (OCD); Dar, David (OC)

**Spokesperson:** Bill Maisel

**Technical Experts:** Michael Bailey (ODE), Geetha Jayan (OCD)

**Medical Expert:** Sheila Murphey (ODE)

**Distribution Plan:**

- o Internal Talking Points distributed to OPA and DSMICA
- o Notify industry via CDRH Twitter
- o Announced in CDRH New
- o Targeted outreach to industry: e-mail/call to AVAMED and Medical Device Manufacturer Association
- o Announced in OSHI Patient and Health Care Newsletters
- o Targeted outreach to medical product purchaser groups and latex organizations/associations through OSHI

***Janesia R. Simmons, MPH, CHES***

Public Health Advisor

Risk Communication Branch

FDA/CDRH/OCE

WO-Bldg. 66, Rm. 4558

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Phone: 301-796-5854

Email: [janesia.simmons@fda.hhs.gov](mailto:janesia.simmons@fda.hhs.gov)

Website: [www.fda.gov](http://www.fda.gov)

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JEANNETTE L O'DONNELL  
12/21/2015  
archiving CMC (b) (4) comments

**From:** O'Donnell, Jeannette  
**To:** "[Santoro, Amanda C](#)"  
**Subject:** FDA Communication: NDA 204016/zoledronic acid/label - Time Sensitive  
**Date:** Thursday, December 17, 2015 12:42:00 PM  
**Importance:** High

---

In reference to NDA 204016, November 2, 2015, class 1 re-submission we have the following labeling comment:

- FDA has stringent requirements for the claim of (b) (4) [redacted] Revise the Prescribing Information (PI) labeling and container labeling to change the term (b) (4) [redacted] to “not made with natural rubber latex” or remove the (b) (4) [redacted] statements with no replacement.

Please submit these changes by no later than **9:00 am Monday, December 21, 2015**. Please submit by 1) email to facilitate review 2) formal submission to the NDA.

*Sincerely,*

*Jeannette O'Donnell*

*Regulatory Project Manager*

*Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products*

*OND/CDER/FDA*

*Phone: 240-402-4978*

*Fax: 301-796-9845*

*Email: [Jeannette.Odonnell@fda.hhs.gov](mailto:Jeannette.Odonnell@fda.hhs.gov)*

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/s/

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JEANNETTE L O'DONNELL  
12/17/2015

**From:** O'Donnell, Jeannette  
**To:** ["Santoro, Amanda C"](#)  
**Subject:** FDA Communication: NDA 204016/zoledronic acid/label revision - Time Sensitive  
**Date:** Thursday, December 10, 2015 1:22:00 PM  
**Importance:** High

---

Dear Ms. Santoro,

In reference to NDA 204016, Zoledronic Acid, Class 1 re-submission submitted on November 2, 2015, please revise the carton labeling and the Prescribing Information (PI) labeling to change the term (b) (4) to "single dose," please be sure to make this change throughout the label.

Please submit the revised labeling by no later than COB Monday December 14, 2015.

*Sincerely,*

*Jeannette O'Donnell*

*Regulatory Project Manager*

*Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products*

*OND/CDER/FDA*

*Phone: 240-402-4978*

*Fax: 301-796-9845*

*Email: [Jeannette.Odonnell@fda.hhs.gov](mailto:Jeannette.Odonnell@fda.hhs.gov)*

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JEANNETTE L O'DONNELL  
12/14/2015

**From:** O'Donnell, Jeannette  
**To:** ["Santoro, Amanda C"](#)  
**Subject:** RE: FDA Communication: NDA 204016/zoledronic acid/label revision - Time Sensitive  
**Date:** Thursday, December 10, 2015 3:35:00 PM

---

Hi Amanda,

Yes, It would be appropriate to change that to "Single Dose Only – Discard Unused Portion."

*Thanks,*

*Jeannette O'Donnell*

*Regulatory Project Manager*

*Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products*

*OND/CDER/FDA*

*Phone: 240-402-4978*

*Fax: 301-796-9845*

*Email: [Jeannette.Odonnell@fda.hhs.gov](mailto:Jeannette.Odonnell@fda.hhs.gov)*

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**From:** Santoro, Amanda C [<mailto:Amanda.Santoro@hospira.com>]  
**Sent:** Thursday, December 10, 2015 3:29 PM  
**To:** O'Donnell, Jeannette  
**Subject:** RE: FDA Communication: NDA 204016/zoledronic acid/label revision - Time Sensitive

Dear Ms. O'Donnell,

After reviewing all of the labeling including container, carton, and PI for this product, I noticed that the container label also contains the phrase "(b) (4) Only – Discard Unused Portion."

Accordingly, can I assume that the request below should also be applied to the container label?

Kind regards,

Amanda

---

**From:** O'Donnell, Jeannette [<mailto:Jeannette.Odonnell@fda.hhs.gov>]  
**Sent:** Thursday, December 10, 2015 12:22 PM  
**To:** Santoro, Amanda C  
**Subject:** FDA Communication: NDA 204016/zoledronic acid/label revision - Time Sensitive  
**Importance:** High

Dear Ms. Santoro,

In reference to NDA 204016, Zoledronic Acid, Class 1 re-submission submitted on November 2, 2015, please revise the carton labeling and the Prescribing Information (PI) labeling to change the term (b) (4) to “single dose,” please be sure to make this change throughout the label.

Please submit the revised labeling by no later than COB Monday December 14, 2015.

*Sincerely,*

*Jeannette O'Donnell*

*Regulatory Project Manager*

*Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products*

*OND/CDER/FDA*

*Phone: 240-402-4978*

*Fax: 301-796-9845*

*Email: [Jeannette.Odonnell@fda.hhs.gov](mailto:Jeannette.Odonnell@fda.hhs.gov)*

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JEANNETTE L O'DONNELL  
12/14/2015



NDA 204016

**ACKNOWLEDGE WITHDRAWAL –  
UNAPPROVED APPLICATION**

Hospira, Inc.  
Attention: Amanda Santoro  
275 North Field Dr.  
Dept. 0389, Bldg. H2-2  
Lake Forest, IL 60045

Dear Ms. Santoro:

Please refer to your New Drug Application (NDA) dated October 23, 2015, received October 23, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zoledronic Acid Injection, 0.04 mg/mL.

We also refer to your letter dated November 2, 2015, requesting withdrawal of this application.

In accordance with 21 CFR 314.65 and your letter of November 2, 2015, this application is withdrawn as of November 2, 2015. If you decide to resubmit this application, this withdrawal will not prejudice any future decisions on filing. You may reference information contained in this withdrawn application in any resubmission.

However, because we retain only the archival copy of a withdrawn application, if you have a paper submission, you should resubmit appropriate review copies of all information. Retain the above NDA number for the resubmitted application.

If you have questions, call Jeannette O'Donnell, Regulatory Project Manager, at (240) 402-4978 or email: [Jeannette.odonnell@fda.hhs.gov](mailto:Jeannette.odonnell@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Geoffrey Kim, MD  
Director  
Division of Oncology Products 1  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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/s/  
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GEOFFREY S KIM  
11/20/2015



NDA 204016

**ACKNOWLEDGE -  
CLASS 1 COMPLETE RESPONSE**

Hospira, Inc.  
Attention: Amanda Santoro  
275 North Field Dr.  
Dept. 0389, Bldg. H2-2  
Lake Forest, IL 60045

Dear Ms. Santoro:

We acknowledge receipt on November 2, 2015, of your November 2, 2015, resubmission to your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Zoledronic Acid Injection, Intravenous Solution, 0.04 mg/mL.

We consider this resubmission a complete, class 1 response to our action letter. Therefore, the user fee goal date is January 2, 2016.

If you have any questions, call me, at (240) 402-4978 or email [Jeannette.Odonnell@fda.hhs.gov](mailto:Jeannette.Odonnell@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Jeannette O'Donnell  
Regulatory Project Manager  
Division of Oncology Products 1  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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/s/  
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JEANNETTE L O'DONNELL  
11/18/2015

**From:** Fagbami, Modupe  
**Sent:** Tuesday, June 18, 2013 11:42 AM  
**To:** 'Santoro, Amanda C'  
**Cc:** Fagbami, Modupe  
**Subject:** RE: NDA 204016 Zoledronic Acid Injection FDA Revised Package Insert  
**Importance:** High

Hi Amanda,

I just left you another message today 6/18/2013.

We are presently preparing towards the action for your NDA 204016 which is due on 7/8/2013.

Kindly send me the updated PI as I requested below by latest COB, tomorrow 6/19/2013.

I am also requesting your response regarding the FDA IR letter of June 3, 2013. Please send the response to the Agency by latest COB, Friday, June 21, 2013.

Please let me know if you have any questions and kindly acknowledge receipt of this e-mail.

Thank you.

Modupe

---

**From:** Fagbami, Modupe  
**Sent:** Monday, June 17, 2013 2:28 PM  
**To:** 'Santoro, Amanda C'  
**Subject:** RE: NDA 204016 Zoledronic Acid Injection FDA Revised Package Insert  
**Importance:** High

Hi Amanda,

Please remove the (b) (4) - from the footnote of the June 6, 2013, PI and resubmit ASAP

I just let you a message. Please call me urgently on (b) (4)

Thank you

Modupe

---

**From:** Santoro, Amanda C [mailto:Amanda.Santoro@hospira.com]  
**Sent:** Thursday, June 06, 2013 6:26 PM  
**To:** Fagbami, Modupe  
**Cc:** Wojtko, Laurie M.; Zboril, Lisa; Fantozzi, Fred  
**Subject:** RE: NDA 204016 Zoledronic Acid Injection FDA Revised Package Insert  
**Importance:** High

Dear Ms. Fagbami,

Please find attached a courtesy copy of the revised package insert per the request below. In addition, please note that this response was also sent through the Electronic Submission Gateway today, June 6, 2013.

If you have any questions that require immediate attention June 7-13, please contact Fred Fantozzi (224-212-4763) as I will be out of the office during this time.

Regards,  
Amanda

**From:** Fagbami, Modupe [mailto:Modupe.Fagbami@fda.hhs.gov]  
**Sent:** Monday, June 03, 2013 5:16 PM  
**To:** Santoro, Amanda C  
**Subject:** NDA 204016 Zoledronic Acid Injection FDA Revised Package Insert  
**Importance:** High

Hi Amanda,

Please note that the Agency found all your updates to the zoledronic acid Injection package insert of January 8, 2013, acceptable. However, minor editorial updates were made as show in the attached.

Kindly review and submit the updated PI by latest COB, Thursday, June 6, 2013.

Thank you

*Modupe O. Fagbami*  
*RPM*  
*Division of Oncology Products 1*  
*Office of Hematology and Oncology Products*  
*CDER, FDA*  
*10903 New Hampshire Avenue*  
*WO-22, Room 2108*  
*Silver Spring, Maryland 20993*  
*Phone: 301-796-1348*  
*Fax: 301-796-9845*

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/s/  
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MODUPE O FAGBAMI  
06/18/2013



MEMORANDUM

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

**DATE:** June 3, 2013

**TO:** Hospira's 505(b)(2) New Drug Application (NDA) for zoledronic acid (NDA 204016)

**FROM:** Robert L. Justice, M.D., M.S.; Director, DOP1

**SUBJECT:** Certification Regarding '241 Patent

**APPLICATION/DRUG:** NDA 204016, zoledronic acid injection, 4 mg/100 mL

This memorandum documents our conclusion regarding whether Hospira must submit to its new drug application (NDA) for zoledronic acid injection, 4 mg/100 mL, a patent certification for Patent No. 7,932,241 ("the '241 patent"). This issue has been the subject of multiple communications between the Agency and Hospira. After considering the available information, we conclude that Hospira must submit a certification with respect to the '241 patent.

### **Background**

#### **Zometa (zoledronic acid) injection (NDA 021223)**

On August 20, 2001, FDA initially approved an NDA for Zometa (zoledronic acid) injection, 4 mg/vial (NDA 021223), for which Novartis Pharmaceuticals Corporation ("Novartis") is the sponsor. FDA subsequently approved two other presentations of Zometa: the 4 mg/5 mL presentation on March 7, 2003; and the 4 mg/100 mL presentation on June 17, 2011. The *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book") currently lists the 4 mg/vial presentation in the discontinued section, and the other two presentations in the active section. The Orange Book lists the '241 patent *only* for the 4 mg/100 mL presentation. According to the Orange Book, the '241 patent expires on February 5, 2028.

### Hospira's proposed zoledronic acid injection

On January 31, 2012, Hospira submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the Act) an NDA for zoledronic acid injection, 4 mg/100 mL (NDA 204016).

Hospira's 505(b)(2) NDA identified *only* the 4 mg/5 mL presentation of Zometa as the listed drug upon which it relies for approval and included one certification for a patent listed for that presentation (i.e., the 4,939,130 or '130 patent).<sup>1</sup> Hospira did not identify the 4 mg/100 mL presentation of Zometa as a listed drug, nor did it include a certification with respect to the '241 patent (which, as noted above, is listed only for that presentation).

On October 15, 2012, and October 24, 2012, the Agency sent an Information Request and follow-up request, respectively. The latter noted that the 4 mg/100 mL presentation of Zometa is a pharmaceutical equivalent to its proposed product and asked Hospira to submit a patent certification with respect to the '241 patent.

On October 31, 2012, Hospira responded by submitting a paragraph III certification to the '241 patent, but "without any admission that it is required to do so". On December 19, 2012, Hospira submitted correspondence requesting that the Agency "withdraw its requirement that Hospira submit a certification or statement as to the '241 patent, as such requirement is not supported in applicable statutes or regulations." On January 15, 2013, Hospira sent by email additional information in support of its position.

### **Summary of Legal Framework**

#### Abbreviated Approval Pathways for Drugs Under the Act

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) created sections 505(b)(2) and 505(j) of the Act.<sup>2</sup>

Section 505(j) of the Act established an abbreviated approval pathway for a drug product that is the same as a previously approved drug (the reference listed drug or RLD)<sup>3</sup> with respect to

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<sup>1</sup> Another patent was subsequently listed for this presentation (i.e., 8,324,189 or '189 patent). Hospira has acknowledged orally the need to certify as to the '189 patent.

<sup>2</sup> The Hatch-Waxman Amendments reflect Congress's efforts to balance the need to "make available more low cost generic drugs by establishing a generic drug approval procedure for pioneer drugs first approved after 1962" with new incentives for drug development in the form of marketing exclusivity and patent term extensions. See House Report No. 98-857, part 1, at 14-15 (1984), reprinted in 1984 U.S.C.A.N. 2647 at 2647-2648.

<sup>3</sup> As defined at 21 C.F.R. 314.3(b), reference listed drug means "the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application."

active ingredient, dosage form, route of administration, strength, and (with certain exceptions) labeling. An ANDA applicant also must demonstrate that its proposed product is bioequivalent to the RLD. An ANDA applicant that meets the requirements under section 505(j) of the Act for approval may reference the Agency's finding of safety and effectiveness for the RLD and need not repeat the extensive nonclinical and clinical investigations required for approval of a stand-alone NDA submitted under section 505(b)(1) of the Act (i.e., an application which contains full reports of investigations of safety and effectiveness).

An ANDA must include an appropriate patent certification or statement for each patent that claims the listed drug to which the applicant refers or a method of using the drug for which the applicant is seeking approval and for which information is required to be filed under section 505(b)(1) or 505(c)(2) of the Act (sections 505(j)(2)(A)(vii)-(viii) of the Act).

Section 505(b)(2) of the Act describes an application that contains full reports of investigations of safety and effectiveness, where at least some of the information required for approval comes from studies that "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted" (section 505(b)(2) of the Act). If the 505(b)(2) NDA seeks to rely on the Agency's previous finding of safety or effectiveness for a listed drug or drugs, under FDA regulations, the 505(b)(2) NDA must identify "the listed drug for which FDA has made a finding of safety and effectiveness and on which the applicant relies in seeking approval of its proposed product . . . ." (21 C.F.R. 314.54(a)(1)(iii)). Like an ANDA, a 505(b)(2) NDA must also include the following:

a certification, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which claims the drug for which such investigations were conducted or which claims a use for such drug for which the applicant is seeking approval under this subsection and for which information is required to be filed under paragraph (1) or subsection (c) of this section. . . .

(Section 505(b)(2)(A) of the Act; see also, 21 C.F.R. 314.54(a), 21 C.F.R. 314.54(a)(1)(vi), and 21 C.F.R. 314.50(i)(1)(i)(A)).<sup>4</sup>

Section 505(b)(2) of the Act explicitly links the drug relied on for approval to the drug for which patent certifications must be made. The Agency's draft Guidance for Industry Applications Covered by Section 505(b)(2) (505(b)(2) Draft Guidance) reflects the Agency's current thinking on the appropriate listed drug upon which a 505(b)(2) applicant may rely in the first instance and

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<sup>4</sup> With respect to each patent as to which the section 505(b)(2) applicant must certify, the certification must state:  
(i) that such patent information has not been filed,  
(ii) that such patent has expired,  
(iii) the date on which such patent will expire, or  
(iv) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted (section 505(b)(2)(A) of the Act).

patent certification obligations that flow from such reliance. The 505(b)(2) Draft Guidance (at p. 8) provides that “[i]f there is a listed drug that is the pharmaceutical equivalent to the drug proposed in the 505(b)(2) application, that drug should be identified as the listed drug.” It further provides (at p. 8) that, “if there is a listed drug that is the pharmaceutical equivalent of the drug proposed in the 505(b)(2) application, the 505(b)(2) applicant should provide patent certifications for the patents listed for the pharmaceutically equivalent drug.”<sup>5</sup>

FDA regulations state that the Agency may refuse to file an application if the application is submitted as a 505(b)(2) application for a drug that is a duplicate<sup>6</sup> of a listed drug and is eligible for approval under section 505(j) of the Act (21 C.F.R. 314.101(d)(9)). Under these provisions, certain products that are pharmaceutically equivalent to and even some “duplicates” of a listed drug may, nevertheless, be inappropriate for review and approval under 505(j) and are permitted to seek approval through the 505(b)(2) pathway instead because, for example, the pharmacokinetic profile is intentionally different from the listed drug or the drug contains an excipient that is not eligible for approval through the 505(j) pathway.<sup>7</sup>

Although 505(b)(2) applications may be received for pharmaceutically equivalent or duplicate products in limited circumstances, at the same time, the above provisions ensure that the 505(b)(2) applicant does not use the 505(b)(2) process to circumvent the patent certification obligations that would have applied under 505(j). Thus, an applicant may not make minor adjustments to a proposed product that would have otherwise been eligible for submission under section 505(j) of the Act and use the differences to avoid certifying to the patents on the pharmaceutically equivalent drug product. Instead, 505(b)(2) applicants are expected to certify to the patents for the pharmaceutically equivalent drug product, even when they did not explicitly seek to rely on that product for approval. These provisions further ensure that the 505(b)(2) applicant (and FDA) can rely, to the maximum extent possible, on what is already known about a drug without having to re-prove (or re-review) what has already been demonstrated.

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<sup>5</sup> See 21 C.F.R. 320.1(c) (defining pharmaceutical equivalents); see also Orange Book (at vi-vii) stating that “[d]rug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), are of the same dosage form, route of administration and are identical in strength or concentration . . . . Pharmaceutically equivalent drug products are formulated to contain the same amount of active ingredient in the same dosage form and to meet the same or compendial or other applicable standards (i.e., strength, quality, purity, and identity), but they may differ in [certain] characteristics” not relevant here.

<sup>6</sup> The term “duplicate” generally refers to a drug product that has the same active ingredient(s), dosage form, strength, route of administration, and conditions of use as a listed drug. See Abbreviated New Drug Application Regulations; Proposed Rule (54 FR 28872 at 28877, July 10, 1989). Thus, the term “duplicate” is often used to refer to a pharmaceutically equivalent drug product that also has the same conditions of use as a previously approved drug product.

<sup>7</sup> Compare 21 C.F.R. 314.54(b) (describing situations in which a 505(b)(2) application may not be submitted).

## **Discussion**

The crux of Hospira's position is that although there is a pharmaceutically equivalent product in Zometa's product line, its 505(b)(2) NDA for proposed zoledronic acid injection, 4 mg/100 mL, relies on only one listed drug -- the 4 mg/5 mL presentation of Zometa (a pharmaceutical alternative). Hospira contends that the Act, implementing regulations, and 505(b)(2) Draft Guidance do not require Hospira to rely on any additional listed drug(s) (see Hospira's December 19, 2012, communication).

As noted above, section 505(b)(2) of the Act explicitly links the drug relied on for approval to the drug for which patent certifications must be made. The Act is silent on the drug(s) on which a 505(b)(2) applicant may rely. FDA regulation state, in part, that the 505(b)(2) NDA must identify "the listed drug . . . on which the applicant relies in seeking approval of its proposed product." (See 21 C.F.R. 314.54(a)(1)(iii)). The 505(b)(2) Draft Guidance clarifies that, if there is a listed drug that is the pharmaceutical equivalent to the drug proposed in the 505(b)(2) NDA, then that drug should be identified as a listed drug and the 505(b)(2) applicant should provide patent certifications for the patents listed for the pharmaceutically equivalent drug.

Despite Hospira's claim, we conclude that for its proposed zoledronic acid injection product, 4 mg/100 mL, Hospira must certify to the patents for the 4 mg/100 mL presentation of Zometa, because its proposed product is pharmaceutically equivalent to that listed drug. Although Hospira states that the 505(b)(2) Draft Guidance is in draft form and not binding, it reflects the Agency's current thinking on the appropriate drug(s) upon which 505(b)(2) applicants may rely and patent certification implications that flow from such reliance. The Agency's interpretation of the Act takes into account not only the relevant statutory provisions, but also the Hatch-Waxman statutory scheme as a whole. As noted above, the Agency's interpretation ensures that the 505(b)(2) applicant does not use the 505(b)(2) process to circumvent the patent certification obligations that would have applied had the application been submitted under 505(j) of the Act, by making certain adjustments to a proposed product that would have otherwise been a duplicate eligible for submission under section 505(j) of the Act.<sup>8</sup>

Because FDA is not in a position to scrutinize an individual company's reasons for choosing a particular listed drug to reference, it has established a bright line approach to listed drugs and

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<sup>8</sup> This position is consistent with the previous explanations of Agency policy on 505(b)(2) NDAs, pharmaceutical equivalents, and patent certification obligations as set forth in Agency decisions (i.e., citizen petition responses). See Letter from Steven K. Galson, M.D., M.P.H., Acting Director, Center for Drug Evaluation and Research, to Donald O. Beers, Arnold & Porter, et. al., Docket No. 2004P-0386 (November 30, 2004) (stating that patent certifications to pharmaceutical equivalents would "ensure that the 505(b)(2) applicant does not use the 505(b)(2) process to end-run patent protections that would have applied had an ANDA been permitted . . ." and that "[t]hey further ensure that the 505(b)(2) applicant (and FDA) can rely, to the maximum extent possible, on what is already known about a drug without having to re-prove (or re-review) what has already been demonstrated"); Letter from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, to Gary L. Veron, Esq., Sidley Austin LLP, Docket No. FDA-2010-P-0614 (May 25, 2011).

patent certifications where there is an approved pharmaceutically equivalent drug product. As noted above, to preserve the integrity of the 505(b)(2) pathway and ensure that it is not used to circumvent patent certification obligations that would have applied for a product submitted under section 505(j) of the Act, FDA has consistently expected 505(b)(2) applicants to certify to the patents for a pharmaceutically equivalent drug product if there is one, regardless of whether the 505(b)(2) applicant seeks to do so.

In support of its position, Hospira maintains that it conducted bioequivalence and stability studies using the 4 mg/5 mL presentation (see Hospira’s January 15, 2013, email). Hospira’s studies using the 4 mg/5 mL presentation are merely evidence of the fact that the 505(b)(2) NDA also relies upon the 4 mg/5 mL presentation of Zometa in seeking approval. This fact does not speak to reliance on other listed drug(s).

Hospira also states that its 4 mg/100 mL proposed zoledronic acid injection is “chemically and pharmaceutically most like” the 4 mg/5 mL presentation of Zometa (see Hospira’s January 15, 2013, email). A comparison of all three formulations is listed in the table below:

<b>4 mg/100 mL (Zometa; ready to use)</b>	<b>4 mg/5 mL (Zometa)</b>	<b>4 mg/100 mL (Hospira; (b) (4))</b>
4.264 zoledronic acid	4.264 zoledronic acid	4.264 zoledronic acid
5100 mg mannitol (bulking agent)	220 mg mannitol (bulking agent)	220 mg mannitol
Water for injection	Water for injection	900 mg sodium chloride in Water for injection (admixture)
24 mg sodium citrate (buffer)	24 mg sodium citrate (buffer)	24 mg sodium citrate
	Dilute with sodium chloride or dextrose solution	

Hospira’s proposed zoledronic acid injection product, 4 mg/100 mL, is pharmaceutically equivalent to the 4 mg/100 mL presentation of Zometa, but it is not pharmaceutically equivalent to the 4 mg/5 mL presentation because its proposed product is a different strength than the 4

mg/5 mL presentation.<sup>9</sup> Further, we also determined that Hospira's proposed product would not qualify for submission as an ANDA for either formulation.<sup>10</sup> The underlying purpose of the Hatch-Waxman Amendments would be undermined by allowing a 505(b)(2) applicant to circumvent patent certification obligations that would be expected to attach to an application submitted under 505(j) by virtue of such changes to formulations that take it out of the 505(j) process.<sup>11</sup>

Hospira states that, after the approval of the 4 mg/100 mL presentation of Zometa in June 2011, it sought and received confirmation from the Division in September 2011 regarding its "strategy, including use of the 4 mg/5 mL" product as its listed drug (see Hospira's January 15, 2012, email). The January 12, 2012, letter from the Agency to Hospira indicates that a "505(b)(2) application would be an acceptable approach at this time based on the information provided." (January 12, 2012, letter from FDA). It also notes that, "if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a duplicate of that drug and eligible for approval under section 505(j) of the [Act], we may refuse to file your application as a 505(b)(2) application" (Id.).

The letter is consistent with our view that Hospira's 505(b)(2) NDA has been properly submitted under the 505(b)(2) pathway because, even though it is a pharmaceutical equivalent of the 4 mg/100 mL product, it is not eligible for approval under section 505(j) as discussed above. The letter is silent on the need to identify additional listed drug(s) and patent certifications. Although we recognize that the Agency could have been more explicit and perhaps should have identified the need for Hospira to identify the 4 mg/100 mL presentation of Zometa as a listed drug and submit relevant patent certifications, this silence does not relieve Hospira of its obligation to identify the appropriate listed drug(s) upon which it relies and certify to relevant patents, including patents on any pharmaceutically equivalent drug products.

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<sup>9</sup> The Orange Book (vii) states that for parenteral drug products "strength" takes into account concentration and total drug content. Hospira's proposed product is a different strength than the 4 mg/5 mL presentation.

<sup>10</sup> FDA regulations (at 21 C.F.R. 314.94(a)(9)(iii)) on drug products intended for parenteral use require that the proposed product contain the same inactive ingredients and in the same concentration as the reference listed drug with the exception of certain excipients (i.e., antioxidant, buffer, preservative). Specifically, Hospira's proposed product has a different amount of mannitol than the 4 mg/100 mL presentation of Zometa and has an admixture (b) (4) that is not present in the 4 mg/5 mL presentation of Zometa. Mannitol and the admixture (b) (4) are not considered exception excipients and therefore submission of an ANDA would not have been permitted.

<sup>11</sup> Although Hospira claims that it selected the 4 mg/5 mL presentation without intending to circumvent the patent certification provisions (see Hospira's January 15, 2013, email), the end result would be the same. It would also be untenable for FDA to take into account an applicant's intent in implementing these provisions.

Finally, Hospira speculates, based on a tentative approval of another company's 505(b) NDA (i.e., (b)(4) 505(b)(2)(NDA)), that (b)(4) did not certify to the '241 patent. Contrary to Hospira's assumption, (b)(4) submitted a paragraph IV certification with respect to the '241 patent. Likewise, other 505(b)(2) applicants for proposed zoledronic acid injection products that are pharmaceutically equivalent to the 4 mg/100 mL presentation of Zometa would also be expected to submit an appropriate certification with respect to the '241 patent.

In sum, we conclude that Hospira must identify the 4 mg/5 mL presentation of Zometa as a listed drug and submit a certification with respect to the '241 patent.

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/s/  
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MODUPE O FAGBAMI  
06/03/2013

ALICE KACUBA  
06/03/2013  
Signing for Frank Cross.

ROBERT L JUSTICE  
06/03/2013



NDA 204016

**INFORMATION REQUEST**

Hospira, Inc.  
Attention: Amanda Santoro  
Senior Associate, Global Regulatory Affairs  
275 North Field Drive  
Dept. 0389, Bldg. H2-2  
Lake Forest, IL 60045

Dear Ms. Santoro:

Please refer to your New Drug Application (NDA) submitted on January 31, 2012, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for zoledronic acid injection, 4 mg/100 mL.

Hospira's 505(b)(2) NDA identified *only* the 4 mg/5 mL presentation of Zometa (zoledronic acid) injection (NDA 021223) as the listed drug upon which it relies for approval and included one certification for a patent listed for that presentation (i.e., the 4,939,130 or '130 patent).<sup>1</sup> On October 15, 2012, and October 24, 2012, the Agency sent an Information Request and follow-up request, respectively. The latter noted that the 4 mg/100 mL presentation of Zometa is a pharmaceutical equivalent to Hospira's proposed product and asked Hospira to submit a patent certification with respect to Patent No. 7,932,241 ("the '241 patent"). On October 31, 2012, Hospira responded by submitting paragraph III certification to the '241 patent but "without any admission that it is required to do so."

On December 19, 2012, Hospira requested that the Agency "withdraw its requirement that Hospira submit a certification or statement as to the '241 patent" for the pharmaceutically equivalent listed drug. Hospira also submitted through its counsel additional information by electronic mail (e-mail) dated January 15, 2013.

After carefully considering the available information, we conclude that Hospira must submit a certification with respect to the '241 patent. This conclusion is consistent with the Federal Food, Drug, and Cosmetic Act (the Act), implementing regulations, Agency guidance, the statutory scheme as a whole, and previous Agency statements set forth in citizen petitions.

Section 505(b)(2) of the Act explicitly links the drug relied on for approval to the drug for which patent certifications must be made. The Act is silent on the drug(s) on which a 505(b)(2) applicant may rely. FDA regulation state, in part, that the 505(b)(2) NDA must identify "the

<sup>1</sup> Another patent was subsequently listed for this presentation (i.e., 8,324,189 or '189 patent).

listed drug . . . on which the applicant relies in seeking approval of its proposed product.” (See 21 C.F.R. 314.54(a)(1)(iii)). The Agency’s draft Guidance for Industry *Applications Covered by Section 505(b)(2)* (1999) clarifies that, if there is a listed drug that is the pharmaceutical equivalent to the drug proposed in the 505(b)(2) NDA, then that drug should be identified as a listed drug and the 505(b)(2) applicant should provide patent certifications for the patents listed for the pharmaceutically equivalent drug.

FDA regulations state that the Agency may refuse to file an application if the application is submitted as a 505(b)(2) application for a drug that is a duplicate<sup>2</sup> of a listed drug and is eligible for approval under section 505(j) of the Act (21 C.F.R. 314.101(d)(9)). Under these provisions, certain products that are pharmaceutically equivalent to and even some "duplicates" of a listed drug may, nevertheless, be inappropriate for review and approval under 505(j) and are permitted to seek approval through the 505(b)(2) pathway instead because, for example, the pharmacokinetic profile is intentionally different from the listed drug or the drug contains an excipient that is not eligible for approval through the 505(j) pathway.<sup>3</sup>

Although 505(b)(2) applications may be received for pharmaceutically equivalent or duplicate products in limited circumstances, at the same time, the above provisions ensure that the 505(b)(2) applicant does not use the 505(b)(2) process to circumvent the patent certification obligations that would have applied under 505(j). Thus, an applicant may not make minor adjustments to a proposed product that would have otherwise been eligible for submission under section 505(j) of the Act and use the differences to avoid certifying to the patents on the pharmaceutically equivalent drug product. Instead, 505(b)(2) applicants are expected to certify to the patents for the pharmaceutically equivalent drug product, even when they do not explicitly seek to rely on that product for approval.

Because FDA is not in a position to scrutinize an individual company’s reasons for choosing a particular listed drug to reference, it has established a bright line approach to listed drugs and patent certifications where there is an approved pharmaceutically equivalent drug product. These provisions further ensure that the 505(b)(2) applicant (and FDA) can rely, to the maximum extent possible, on what is already known about a drug without having to re-prove (or re-review) what has already been demonstrated. This position is consistent with the previous explanations of Agency policy on 505(b)(2) NDAs, pharmaceutical equivalents, and patent certification obligations as set forth in Agency decisions (i.e., citizen petition responses).<sup>4</sup>

In support of its position, Hospira maintains that it conducted bioequivalence and stability studies using the 4 mg/5 mL presentation (see Hospira’s January 15, 2013, e-mail). Hospira’s

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<sup>2</sup> The term “duplicate” generally refers to a drug product that has the same active ingredient(s), dosage form, strength, route of administration, and conditions of use as a listed drug. See *Abbreviated New Drug Application Regulations; Proposed Rule* (54 FR 28872 at 28877, July 10, 1989). Thus, the term “duplicate” is often used to refer to a pharmaceutically equivalent drug product that also has the same conditions of use as a previously approved drug product.

<sup>3</sup> Compare 21 C.F.R. 314.54(b) (describing situations in which a 505(b)(2) application may not be submitted).

<sup>4</sup> See e.g., Letter from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, to Gary L. Veron, Esq., Sidley Austin LLP, Docket No. FDA-2010-P-0614 (May 25, 2011).

studies using the 4 mg/5 mL presentation are merely evidence of the fact that the 505(b)(2) NDA also relies upon the 4 mg/5 mL presentation of Zometa in seeking approval. This fact does not speak to reliance on other listed drug(s).

Hospira also states that its 4 mg/100 mL proposed zoledronic acid injection is “chemically and pharmaceutically most like” the 4 mg/5 mL presentation of Zometa (see Hospira’s January 15, 2013, e-mail). However, Hospira’s proposed zoledronic acid injection product, 4 mg/100 mL, is pharmaceutically equivalent to the 4 mg/100 mL presentation of Zometa, but it is not pharmaceutically equivalent to the 4 mg/5 mL presentation because its proposed product is a different strength than the 4 mg/5 mL presentation. Further, we also determined that Hospira’s proposed product would not qualify for submission as an ANDA for either formulation. The underlying purpose of the Hatch-Waxman Amendments would be undermined by allowing a 505(b)(2) applicant to circumvent patent certification obligations that would be expected to attach to an application submitted under 505(j) by virtue of making certain changes to formulations that take it out of the 505(j) process.<sup>5</sup>

Hospira states that, after the approval of the 4 mg/100 mL presentation of Zometa in June 2011, it sought and received confirmation from the Division in September 2011 regarding its “strategy, including use of the 4 mg/5 mL” product as its listed drug (see Hospira’s January 15, 2012, e-mail). The January 12, 2012, letter from the Agency to Hospira indicates that a “505(b)(2) application would be an acceptable approach at this time based on the information provided” (January 12, 2012, letter from FDA). It also notes that, “if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a duplicate of that drug and eligible for approval under section 505(j) of the [Act], we may refuse to file your application as a 505(b)(2) application” (Id.).

The letter is consistent with our view that Hospira’s 505(b)(2) NDA has been properly submitted under the 505(b)(2) pathway because, even though it is a pharmaceutical equivalent of the 4 mg/100 mL product, it is not eligible for approval under section 505(j) as discussed above. The letter is silent on the need to identify additional listed drug(s) and patent certifications. Although we recognize that the Agency could have been more explicit in identifying the need for Hospira to cite the 4 mg/100 mL presentation of Zometa as a listed drug and submit relevant patent certifications, this silence does not relieve Hospira of its obligation to identify the appropriate listed drug(s) upon which it relies and certify to relevant patents, including patents on any pharmaceutically equivalent drug products.

Finally, Hospira speculates, based on a tentative approval of another company’s 505(b)(2) NDA (i.e., (b)(4) 505(b)(2)(NDA)), that (b)(4) did not certify to the ‘241 patent. Although we cannot disclose information regarding another application, we note that 505(b)(2) applicants for proposed zoledronic acid injection products that are pharmaceutically equivalent to the 4 mg/100 mL presentation of Zometa would also be expected to submit an appropriate certification with respect to the ‘241 patent.

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<sup>5</sup> Although Hospira states that it selected the 4 mg/5 mL presentation without intending to circumvent the patent certification provisions (see Hospira’s January 15, 2013, e-mail), the end result would be the same.

In conclusion, Hospira must submit a certification with respect to the '241 patent. In addition, Hospira has not yet submitted a certification to the '189 patent and must do so.

If you have any questions, call Modupe Fagbami, Regulatory Project Manager, at (301) 796-1348.

Sincerely,

*{See appended electronic signature page}*

Robert L. Justice, M.D., M.S.  
Director  
Division of Oncology Products 1  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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/s/  
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ROBERT L JUSTICE  
06/03/2013

**From:** Fagbami, Modupe  
**Sent:** Monday, June 03, 2013 6:16 PM  
**To:** 'Santoro, Amanda C'  
**Subject:** NDA 204016 Zoledronic Acid Injection FDA Revised Package Insert  
**Importance:** High

Hi Amanda,

Please note that the Agency found all your updates to the zoledronic acid Injection package insert of January 8, 2013, acceptable.



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-8-2013.doc (39.

However, minor editorial updates were made as show in the attached.

Kindly review and submit the updated PI by latest COB, Thursday, June 6, 2013.

Thank you

*Modupe O. Fagbami*

*RPM*

*Division of Oncology Products 1*

*Office of Hematology and Oncology Products*

*CDER, FDA*

*10903 New Hampshire Avenue*

*WO-22, Room 2108*

*Silver Spring, Maryland 20993*

*Phone: 301-796-1348*

*Fax: 301-796-9845*

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/s/  
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MODUPE O FAGBAMI  
06/03/2013

MEMORANDUM

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

**DATE:** February 6, 2013

**Time:** 10:00 am

**Location:** WO, Building 22, Room 5201

**Memorandum of Teleconference between**

**FDA:**

Ali Al-Hakim, Ph.D., CMC Branch Chief, ONDQA  
Li-Shan Hsieh, Ph.D., CMC Reviewer, ONDQA,  
Haripada Sarker, Ph.D., CMC Lead, ONDQA, DNDQA I  
Genevieve Schechter, M.D. Clinical Reviewer, DOP1  
Mahesh Ramanadham, PharmD, M.B. A., Regulatory Compliance Officer, OC/OMPQ  
Modupe Fagbami, Regulatory Project Manager, DOP1

**And**

**Hospira Inc.:**

Lisa Skeens, Ph.D., VP Global Regulatory Affairs  
Janet Stevens, VP Quality Operations  
Lisa Zboril, R.Ph., Sr. Director, Global Regulatory Affairs  
Amanda Santoro, Sr. Associate, Global Regulatory Affairs

**SUBJECT:** Discussion on the FDA's rationale for categorizing Applicant's submission of January 8, 2013 as a Resubmission Class 2.

**APPLICATION/DRUG:** NDA 204016, Zoledronic Acid Injection, 4mg/mL

**BACKGROUND:**

The applicant submitted a complete response on January 8, 2013, to the FDA as a Class 1 resubmission, in response to the FDA's Complete Response letter issued on November 29, 2012.

In response to the Agency's acknowledgement letter of January 29, 2013, in which the submission was reclassified as a Class 2 resubmission, the applicant requested to understand the rationale for the reclassification to a Class 2 resubmission at a discussion with the Agency by teleconference.

**Summary of Teleconference:**

**FDA:**

FDA recognized the request to clarify the rationale for a class 2 resubmission vs. class 1 resubmission and recognized the DEN-DO's January 7, 2013, communication to the applicant. FDA stated that while DEN-DO communicated its recommendation to Hospira Inc., the final recommendation is made by CDER/Office of Compliance.

FDA clarified that the decision to classify the submission as a class 2 resubmission was based on the need to evaluate facility compliance in response to the resubmission. The evaluation may necessitate a facility inspection which will warrant a 6 month clock. FDA clarified that while the 6 month clock is an appropriate resubmission classification due to the facility deficiencies in the CR letter, action may be taken sooner if possible.

**Applicant:**

The applicant said that the complete response was submitted as a class 1 resubmission in anticipation of an expedited approval of their product and their envisaged planned product launch. The applicant while attesting to respecting the Agency's review process, requested clarification regarding the resubmission classification in response to facility deficiencies.

**FDA:**

The Agency clarified that the current understanding of resubmission classification for facility deficiencies would stipulate a class 2 resubmission, due to the need for a facility compliance evaluation upon resubmission.

The teleconference ended amicably at 10:20 am

Prepared by:

Modupe Fagbami, Regulatory Project Manager, DOP1

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MODUPE O FAGBAMI  
02/12/2013

ALI H AL HAKIM  
02/12/2013

**From:** Fagbami, Modupe  
**Sent:** Monday, February 04, 2013 5:16 PM  
**To:** 'lisa.zboril@hospira.com'  
**Cc:** 'Santoro, Amanda C'  
**Subject:** FW: NDA 204016 Zoledronic Acid Injection 4mg/mL  
**Importance:** High

Dear Lisa,

I am referencing your e-mail below to Captain Cross.

The FDA has agreed to have a t-con with Hospira Inc., Applicant of NDA 204016, to discuss the rationale for re-classifying the submission of January 8, 2013, as a Class 2 Resubmission.

The t-con is scheduled for Wednesday, February 6, 2013 at 10:00 am

Please send me the following by latest 12:00 noon on Tuesday, February 5, 2013. They are: Conference Call phone information and your list of attendees at this t-con.

Kindly let me know if you have any questions

Thank you

Modupe Fagbami

---

**From:** Zboril, Lisa [<mailto:lisa.zboril@hospira.com>]  
**Sent:** Friday, February 01, 2013 4:45 PM  
**To:** Cross Jr, Frank H; Fagbami, Modupe  
**Cc:** Santoro, Amanda C  
**Subject:** NDA 204016 Zoledronic Acid Injection 4mg/mL

Dear Captain Cross,

Thank you for taking my call today.

Hospira acknowledges receipt of the Agency's correspondence dated January 29, 2013 regarding our January 8, 2013 resubmission to the Agency's Complete Response letter dated November 29, 2012. This acknowledgement letter states the Agency considers our Zoledronic Acid Injection resubmission to be a complete, Class 2 response to the November 29, 2012 action letter.

As we discussed, Hospira is trying to understand the basis for the Class 2 designation. In order to address the Facility Inspection deficiency sited in

our Complete Response letter, our resubmission included a written summary stating that satisfactory resolution of the deficiencies from the recent inspection at the Boulder site had been confirmed and that the site status had been changed from OAI to VAI without the need for a re-inspection. This was conveyed to Hospira in a January 7, 2012 correspondence from Mr. Thomas Berry of the FDA Denver District Office, which was provided as an attachment in the resubmission.

Hospira felt this was sufficient to respond to the deficiency and that the response aligned with the intent of the Class 1 resubmission definition.

As you suggested, a teleconference next week to discuss the Agency's basis for classification would be appreciated.

Thank you again for your assistance in this matter.

Best Regards,

Lisa

**Lisa K. Zboril, R.Ph.**

Senior Director, Global Pharma Development

Global Regulatory Affairs

Hospira, Inc.

Office: (224) 212-4654

Cell: (b) (6)

FAX: (224) 212-5402

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/s/  
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MODUPE O FAGBAMI  
02/04/2013



NDA 204016

**ACKNOWLEDGE –  
CLASS 2 RESPONSE**

Hospira Inc.  
Attention: Amanda Santoro  
Senior Associate, Global Regulatory Affairs  
275 North Field Drive  
Dept. 0389, Bldg. H2-2  
Lake Forest, IL 60045

Dear Ms. Santoro:

We acknowledge receipt on January 8, 2013, of your January 8, 2013, resubmission of your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Zoledronic Acid Injection, 4 mg/100 mL.

We consider this a complete, class 2 response to our November 29, 2012, action letter. Therefore, the user fee goal date is July 8, 2013.

If you have any questions, call me at (301) 796-1348.

Sincerely,

*{See appended electronic signature page}*

Modupe Fagbami  
Regulatory Project Manager  
Division of Oncology Products 1  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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/s/  
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MODUPE O FAGBAMI  
01/29/2013

**From:** Fagbami, Modupe  
**Sent:** Wednesday, November 14, 2012 10:20 AM  
**To:** 'Santoro, Amanda C'  
**Subject:** NDA 204016 Zoledronic Acid FDA Revisions to Package Insert  
**Importance:** High

Dear Amanda,

Please find attached the FDA revisions to the PI for NDA 204016. Kindly send me the response to this by latest 12:00 noon, EST, Friday, November 16, 2012.



proposed with  
DA Revisions of..

Kindly let me know if you have any questions.

Thank you

*Modupe O. Fagbami*

*RPM*

*Division of Oncology Products 1*

*Office of Hematology and Oncology Products*

*CDER, FDA*

*10903 New Hampshire Avenue*

*WO-22, Room 2108*

*Silver Spring, Maryland 20993*

*Phone: 301-796-1348*

*Fax: 301-796-9845*

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/s/  
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MODUPE O FAGBAMI  
11/15/2012

## Fagbami, Modupe

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**From:** Liu, Qi (CDER)  
**ent:** Wednesday, November 14, 2012 9:50 AM  
**ro:** Ibrahim, Amna; Fagbami, Modupe; Cross Jr, Frank H; Chidambaram, Nallaperum  
**Cc:** Song, Pengfei  
**Subject:** This is Pengfei's NAI communication in DARRTS. Thanks!

REV-CLINPHARM-02 (Review Noted (NAI))  
NDA-204016  
ORIG-1  
Supporting Document 1  
New/NDA Form 3674  
Submit Date: 01/30/2012 - FDA Received Date: 01/30/2012

-----  
There is no bioequivalent study nor clinical study submitted in this application. The Applicant is relying on the findings of safety and effectiveness for Zometa® to support the approval of the proposed product. No clinical pharmacology issues have been identified.

**From:** Fagbami, Modupe  
**Sent:** Monday, October 15, 2012 4:57 PM  
**To:** 'Santoro, Amanda C'  
**Subject:** NDA 204016 Zoledronic Acid Information Request  
**Importance:** High

Dear Amanda,

Under 21 CFR 314.54(a)(1)(vi), a 505(b)(2) application must contain a patent certification or statement with respect to any relevant patents that claim the listed drug and that claim any other drugs on which the investigations relied on for approval of the application were conducted, or that claim a use for the listed or other drug.

Your 505(b)(2) application relies upon the Agency's finding of safety and effectiveness for NDA 21223 for Zometa (zoledronic acid) injection, but does not contain a patent certification or statement with respect to each patent listed in FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book) for the listed drug upon which you rely (see 21 CFR 314.54(a)(1)(vi)).

The NDA holder for Zometa (zoledronic acid) injection, 4 mg/5mL and 4 mg/100 mL, submitted information on U.S. Patent No. 7,932,241 ('241 patent) for listing in the Orange Book. In accordance with section 505(b)(2) of the FDCA and 21 CFR 314.50(i), you must submit an appropriate patent certification or statement with respect to the '241 patent.

Note that if you choose to submit Paragraph IV certification as described under 21 CFR 314.50(i)(1)(i)(A)(4), you must provide the signed notice of certification of invalidity or noninfringement of a patent and the proof of notification described under 21 CFR 314.52(e).

Kindly respond to this information request on or before COB October 22, 2012.

Please let me know if you have any questions

Thank you

*Modupe O. Fagbami*  
*RPM*  
*Division of Oncology Products 1*  
*Office of Hematology and Oncology Products*  
*CDER, FDA*  
*10903 New Hampshire Avenue*  
*WO-22, Room 2108*  
*Silver Spring, Maryland 20993*  
*Phone: 301-796-1348*  
*Fax: 301-796-9845*

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/s/  
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MODUPE O FAGBAMI  
10/15/2012

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**From:** Skarupa, Lisa  
**Sent:** Monday, September 24, 2012 11:23 AM  
**To:** 'Santoro, Amanda C'  
**Cc:** Fagbami, Modupe; Cottrell, Christy L.; Tilley, Amy  
**Subject:** RE: NDA 204016 FDA Response to Package Insert received Sept 14th

Amanda,  
How soon would your team be able to respond to the comments attached to Friday's email?

Sincerely,  
Lisa

---

**From:** Santoro, Amanda C [mailto:Amanda.Santoro@hospira.com]  
**Sent:** Monday, September 24, 2012 10:31 AM  
**To:** Skarupa, Lisa  
**Cc:** Fagbami, Modupe; Cottrell, Christy L.; Tilley, Amy  
**Subject:** RE: NDA 204016 FDA Response to Package Insert received Sept 14th

Lisa,

The email you sent last Friday was received.

Regards,  
Amanda

**From:** Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]  
**Sent:** Monday, September 24, 2012 9:30 AM  
**To:** Santoro, Amanda C  
**Cc:** Fagbami, Modupe; Cottrell, Christy L.; Tilley, Amy  
**Subject:** RE: NDA 204016 FDA Response to Package Insert received Sept 14th

Dear Amanda,  
Please confirm that you received our response Friday evening,

Thank you  
Lisa

---

**From:** Skarupa, Lisa  
**Sent:** Friday, September 21, 2012 7:22 PM  
**To:** 'Santoro, Amanda C'  
**Cc:** Fagbami, Modupe; Cottrell, Christy L.  
**Subject:** RE: NDA 204016 FDA Response to Package Insert received Sept 14th

Dear Amanda,  
The following is the response to your package insert you sent last Friday.

If you have any questions, please do not hesitate to contact us.

Sincerely,  
Lisa

---

**From:** Santoro, Amanda C [mailto:Amanda.Santoro@hospira.com]  
**Sent:** Friday, September 14, 2012 3:10 PM  
**To:** Fagbami, Modupe  
**Cc:** Skarupa, Lisa  
**Subject:** NDA 204016 FDA Revisions to Applicant's PI and Information Request  
**Importance:** High

Modupe,

Please find attached a courtesy copy of Hospira's responses to the FDA comments that resulted from the teleconference held on September 10, 2012.

Please also note that a formal submission was sent through the Electronic Submission Gateway today.

Regards,  
Amanda

*Amanda Santoro*

Senior Associate  
Global Regulatory Affairs  
Hospira Inc.  
Dept. 389, Building H2  
Lake Forest, IL 60045-5045  
Phone: 224-212-5040 Fax: 224-212-5401  
[Amanda.Santoro@hospira.com](mailto:Amanda.Santoro@hospira.com)

---

**From:** Fagbami, Modupe [mailto:Modupe.Fagbami@fda.hhs.gov]  
**Sent:** Monday, September 10, 2012 5:16 PM  
**To:** Santoro, Amanda C  
**Cc:** Skarupa, Lisa  
**Subject:** NDA 204016 FDA Revisions to Applicant's PI and Information Request  
**Importance:** High

Dear Amanda,

As agreed at the T-con between the FDA and Hospira, Inc. today, September 10, 2012, please find the FDA Revisions to your PI for your response.

In addition, please ensure that you update the PI with the agreed updates from our teleconference as listed below:

The Applicant will update the package insert labeling to include instructions on preparation of renally-adjusted doses with their recommended transfer device and the Applicant agrees to submit the revised package insert labeling to the FDA by 12:00 noon on Friday September 14, 2012.

Also at the meeting today,

The Applicant agreed to provide data that illustrate that the applicant's recommended transfer device is common in all types of facilities that use Zoledronic Acid, such as hospitals and outpatient infusion centers. Additionally, the Applicant will better define the type of transfer device and also list any approved drugs that recommended a similar transfer device in the labeling. The Applicant agreed to submit this data by September 14, 2012.

Kindly copy Lisa Skarupa on the response to this e-mail

Please let me know if you have any questions.

Thank you

***Modupe O. Fagbami***

*RPM*

*Division of Oncology Products 1*

*Office of Hematology and Oncology Products*

*CDER, FDA*

*10903 New Hampshire Avenue*

*WO-22, Room 2108*

*Silver Spring, Maryland 20993*

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NDA 204016  
Zoledronic Acid 4 mg/100 mL bag

Your response to our 9/10/2012 IR does not provide the granularity we need to evaluate your proposal to recommend a transfer device to prepare renally-adjusted doses. Although [REDACTED] (b) (4) publications and there is an estimated \$ [REDACTED] (b) (4) market for [REDACTED] (b) (4), this does not assure us these devices are used by the healthcare practitioners at all types of facilities that use Zoledronic Acid. Furthermore, the package insert labeling does not provide detailed instructions on exactly what type of device to use and how to use it.

To better evaluate your proposal, we request the following:

1. Improve the description of the transfer device. The term [REDACTED] (b) (4) that is used in section 2.3 of the package insert labeling is ambiguous and does not clearly define the intended device. Specify the transfer device, commercial availability, material of construction (e.g., [REDACTED] (b) (4)), and in-use stability data for the duration the drug product will be in contact with the transfer device.
2. Include step-by-step instructions on how to prepare the adjusted doses using the transfer device(s).
3. Provide granular data to illustrate the recommended transfer device(s) is common in all types of facilities that use Zoledronic Acid, such as hospitals, outpatient infusion centers, and private physician office practices.
4. Provide data to show the recommended transfer device(s) are mechanically compatible with the Zoledronic Acid [REDACTED] (b) (4) bag for withdrawal of solution during preparation and administration to the patient.

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/s/  
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LISA M SKARUPA  
09/24/2012

**From:** Tilley, Amy  
**Sent:** Monday, September 24, 2012 4:58 PM  
**To:** 'amanda.santoro@hospira.com'  
**Cc:** Cross Jr, Frank H; Kacuba, Alice; Cottrell, Christy L.; Toaff, Techiya; Fagbami, Modupe  
**Subject:** NDA 204016 Zoledronic Acid Inj - Addtl CMC IR

**Follow Up Flag:** Follow up  
**Due By:** Friday, September 28, 2012 12:00 PM  
**Flag Status:** Completed  
Amanda,

Below is an additional CMC Information Request (IR)

Please respond **no later than Noon on Friday, 9-28-12.**

- Based on drug product batch analysis data, any single unknown and total impurities are shown "none detected" and "0.0%", respectively. However the acceptance criteria for any single unknown and total impurities are set for NMT (b) (4) % and NMT (b) (4) %, respectively, for both release and shelf-life specifications. We recommend that you tighten these acceptance criteria for both release and shelf-life.
- Based on provided drug product stability data, we recommend that you tighten the shelf-life specification for assay from (b) (4) %.
- Provide an updated specification table to reflect above recommended revisions.

Regards.

*Amy Tilley*

---

Amy Tilley | Regulatory Project Manager | Division of Oncology Products  
1,  
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,  
MD 20993  
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov



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/s/  
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AMY R TILLEY  
09/24/2012

**MEMORANDUM OF TELECON**

**DATE:** September 10, 2012      **LOCATION:** White Oak Building 22, Room 2201

**APPLICATION NUMBER:** NDA 204016

**APPLICANT:** Hospira Inc.

**Drug:** Zoledronic Acid Injection, 4 mg/100 mL

**Start Time:** 2:00 p.m.

**End Time:** 3:00 p.m.

**SUBJECT:** Discussion of renally adjusted dosing of Zoledronic Acid Injection, 4 mg/100 mL

**FDA ATTENDEES:**

Amna Ibrahim, M.D., Deputy Director, DOP1/OHOP

Amy McKee, M.D., Lead Medical Officer, DOP1/OHOP

Genevieve Schechter, M.D., Medical Officer, DOP1/OHOP

Haripada Sarker, Ph.D., CMC Lead, DNDQA I/ONDQA

Li Shan Hsieh, Ph.D., CMC Reviewer, DNDQA/ONDQA I

Jibril Abdus-Samad, Pharm. D., Safety Evaluator, OMPT/CDER/OSE/OMEPRM/DMEPA

Todd Bridges, R. Ph., Team Leader, OMPT/CDER/OSE/OMEPRM/DMEPA

Fahnbulleh Frances, Pharm. D., Regulatory Project Manager, OMPT/CDER/OSE/OMEPRM/DMEPA

Modupe Fagbami, Regulatory Project Manager, DOP1/OHOP

**APPLICANT ATTENDEES:**

Mary Baker, Pharm. D., Director, Medical Services, Hospira, Inc.

Brenda Clark, R. N., Training and Development, Hospira, Inc.

John Grillo, Research Scientist, Microbiology, Hospira, Inc.

Andrea Redd, Sr. Program Manager, Hospira, Inc.

Amanda Santoro, Sr. Associate, Global Regulatory Affairs, Hospira, Inc.

Rao Tata-Venkata, Research Scientist, Chemistry, Hospira, Inc.

Lisa Zboril, R. Ph., Director, Global Regulatory Affairs, Hospira, Inc.

**BACKGROUND:**

On September 5, 2012, FDA provided the following Information Request to the Applicant:

The package insert labeling instructs the user to infuse the specified volume via an infusion pump based on the renally-adjusted doses in section 2.3 of the package insert labeling. However, labeling the product to instruct healthcare practitioners to program the infusion pump to deliver partial volumes for a

15 minute infusion is not safe. FDA finds the safest method of administration of renally-adjusted doses is to provide the correct amount of drug in the intravenous bag *prior* to programming the pump and administering to the patient. Thus, we have three options available for you to consider.

1. [REDACTED] (b) (4)  
[REDACTED] Use the currently approved preparation instructions as it appears in the label for the listed drug Zometa (Zoledronic Acid) 4 mg/100 mL bottle.
2. Develop [REDACTED] (b) (4) bags for the recommended renally adjusted doses (3.5 mg, 3.3 mg, and 3 mg). Additionally, it is imperative that you adequately differentiate the strength on the carton and container labels to prevent wrong strength selection errors as the doses look similar.

4 mg/100 mL  
3.5 mg/[REDACTED] (b) (4)  
3.3 mg [REDACTED] (b) (4)  
3 mg/[REDACTED] (b) (4)

2. Revise the container label, carton, and package insert labeling to communicate this product is not intended for use with patients that require renal dose adjustments and therefore, these patients must receive a different Zoledronic Acid product. Additionally, this information should also be noted on a sticker over the tube and twist-off cap portion of the pre-mixed bag so that healthcare practitioners note this warning prior to administration. The length of the statement may require a sticker that has a flap or flange to allow additional space.

#### **Applicant's Proposal Prior to the T-Con:**

Hospira has evaluated the options provided by the Agency and believe that option 1 (above) is most viable pathway forward.

As recommended by the Agency, Hospira proposes to adopt similar language for 1 port bag from the currently approved preparation instructions as it appears in the label for the listed drug Zometa (Zoledronic Acid) 4 mg/100 mL [REDACTED] (b) (4). The withdrawal of the specified volume can be achieved with the use of a commercially available IV transfer device, when needed, for reduced dosing. This will provide the correct amount of drug in the bag prior to pump programming and administration to the patient.

#### **Discussion Points:**

- FDA began the discussion by asking the Applicant to describe specifically what device they were recommending for use with their product. The Applicant provided a description of the device.
- Considering there are various transfer devices, FDA requested the Applicant to consider packaging their recommended device with their Zoledronic Acid product.
- FDA noted 8 practicing inpatient pharmacists in the [REDACTED] (b) (4) area that are not familiar with these transfer devices, but rather transfer devices used in preparation of large volume parenterals or total parenteral nutrition.

- The Applicant provided more background information claiming their recommended transfer device is used in pharmacies regularly for parenteral product preparation and are recommended in publications such as (b)(4). The Applicant estimates their recommended transfer device has been on the market for approximately (b)(4) years.
- FDA noted that the Zoledronic Acid pre-mix IV bag is designed to be infused as is. One important advantage with using pre-mixed bags is elimination of preparation errors. Once Health Care Providers begin to introduce manipulations of a (b)(4) bag, opportunities for preparation errors arise.
- FDA noted their evaluation of the Applicant's proposal is on-going and requested any data to support the Applicant's recommended device as commonly used in all the facilities that are likely to use Zoledronic Acid would be beneficial.

**Action Items:**

- FDA will send the most up-to-date package insert labeling revisions to the Applicant on September 10, 2012.
- The Applicant will update the package insert labeling to include instructions on preparation of renally-adjusted doses with their recommended transfer device. Applicant agreed to submit the revised package insert labeling edits back to FDA by Friday, September 14, 2012.
- The Applicant agreed to provide data that illustrates their recommended transfer device as common in all types of facilities that use Zoledronic Acid, such as hospitals and outpatient infusion centers. Additionally, the Applicant will better define the type of transfer device and also list any approved drugs that recommend a similar transfer device in the labeling. The Applicant agreed to submit this data by September 17, 2012.

The teleconference ended at 3:00 pm

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Modupe Fagbami, RPM, DOP1/OHOP

Haripada Sarker, Ph.D., CMC Lead, DNDQA I/ONDQA

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/s/

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MODUPE O FAGBAMI  
11/16/2012

HARIPADA SARKER  
11/16/2012

**From:** Fagbami, Modupe  
**Sent:** Wednesday, September 05, 2012 5:08 PM  
**To:** 'Santoro, Amanda C'  
**Cc:** Tian, Wendy W.  
**Subject:** NDA 204016 Zoledronic Acid Injection 4 mg/100 mL (0.04 mg/mL) pre-mixed bag Information Request  
**Importance:** High

Hi Amanda,

Please find the following IR for your responses on or before 12:00 noon on Friday, September 7, 2012.

Your responses to these requests will be the basis of the T-con scheduled for Monday, September 10, 2012 at 2: 00 pm.

The package insert labeling instructs the user to infuse the specified volume via an infusion pump based on the renally-adjusted doses in section 2.3 of the package insert labeling. However, labeling the product to instruct healthcare practitioners to program the infusion pump to deliver partial volumes for a 15 minute infusion is not safe. FDA finds the safest method of administration of renally-adjusted doses is to provide the correct amount of drug in the intravenous bag *prior* to programming the pump and administering to the patient. Thus, we have three options available for you to consider.

1. [REDACTED] (b) (4)  
[REDACTED] Use the currently approved preparation instructions as it appears in the label for the listed drug Zometa (Zoledronic Acid) 4 mg/100 mL bottle.
2. Develop [REDACTED] (b) (4) bags for the recommended renally adjusted doses (3.5 mg, 3.3 mg, and 3 mg). Additionally, it is imperative that you adequately differentiate the strength on the carton and container labels to prevent wrong strength selection errors as the doses look similar.

4 mg/100 mL  
3.5 mg/ [REDACTED] (b) (4)  
3.3 mg/ [REDACTED] (b) (4)  
3 mg/ [REDACTED] (b) (4)

3. Revise the container label, carton, and package insert labeling to communicate this product is not intended for use with patients that require renal dose adjustments and therefore, these patients must receive a different Zoledronic Acid product. Additionally, this information should also be noted on a sticker over the tube and twist-off cap portion of the pre-mixed bag so that healthcare practitioners note this warning prior to administration. The length of the statement may require a sticker that has a flap or flange to allow additional space.

Please let me know if you have any questions.

Thank you

*Modupe O. Fagbami*

*RPM*

*Division of Oncology Products 1*

*Office of Hematology and Oncology Products*

*CDER, FDA*

*10903 New Hampshire Avenue*

*WO-22, Room 2108*

*Silver Spring, Maryland 20993*

*Phone: 301-796-1348*

*Fax: 301-796-9845*

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/s/  
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MODUPE O FAGBAMI  
09/05/2012

**From:** Fagbami, Modupe  
**Sent:** Tuesday, August 28, 2012 9:50 AM  
**To:** 'Santoro, Amanda C'  
**Subject:** NDA 204016 Zoledronic Acid Container Carton Information Request  
**Importance:** High

Dear Amanda,

Please find the following Container and Carton Information Requests for your response on or before 12:00 noon, Friday, September 7, 2012.

#### A. Container Label

1. Revise the font size and weight of the word *Injection* to match *Zoledronic Acid*.
2. Move the infusion time statement, *Infusion time must not be less than 15 minutes*, to appear directly below the statement, *Do not mix with calcium-containing solutions*.
3. To remove clutter and improve readability by creating space for increased prominence of important information, revise the label as follows:

- a. Revise the statement, (b) (4)  
(b) (4) to read as follows:  
See insert for dosage and administration.

Note deletion of the word (b) (4) and use of lowercase letters for *dosage and administration* to remove clutter, create space, and improve readability of more important information.

- b. Delete the statement, (b) (4)  
(b) (4)
- c. Delete the statement, (b) (4)
4. Revise the statement, (b) (4) to read as follows:  
(b) (4) Only – Discard Unused Portion
5. Add a bar code to be in compliance with 21 CFR 201.25.
6. Revise the storage information to read as follows:

(b) (4)  
Do not freeze.

#### B. Carton Labeling

1. Revise the font size and weight of the word *Injection* to match *Zoledronic Acid*.
2. Add the infusion time statement, *Infusion time must not be less than 15 minutes*, to the principal display panel to appear directly below the statement, *Do not mix with calcium-containing solutions*.
3. Add the statement, (b) (4) Only – Discard Unused Portion, to the principal display panel
4. Revise the storage information to read as follows:

Do not freeze.

Please let me know if you have any questions.

Thank you

*Modupe O. Fagbami*

*RPM*

*Division of Oncology Products 1*

*Office of Hematology and Oncology Products*

*CDER, FDA*

*10903 New Hampshire Avenue*

*WO-22, Room 2108*

*Silver Spring, Maryland 20993*

*Phone: 301-796-1348*

*Fax: 301-796-9845*

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MODUPE O FAGBAMI  
08/28/2012

**From:** Fagbami, Modupe  
**Sent:** Wednesday, August 22, 2012 12:39 PM  
**To:** 'Santoro, Amanda C'  
**Subject:** NDA 204016 Zoledronic acid Injection CMC Micro Information Request  
**Importance:** High

Hi Amanda,

Please find the following CMC Information Request for your response on or before COB, Wednesday, August 29, 2012.

In section 2.2 of the proposed draft labeling, you have included dose reductions for renal impairment but you have not provided instructions on how to perform the dose reductions using the single port on the (b) (4) bag. Please respond to the following information request by noon EST on 8/24:

1. Container-closure: (b) (4)  

2. The drug product is sterile and does not contain a preservative. Since any external penetration of the container/closure system of a sterile drug product provides an opportunity for microbial contamination of that drug product, please provide labeling text stating that the drug product (b) (4)  

3. Please provide labeling text regarding the preparation of reduced doses for patients with renal impairment in line with section 2.3 of the ZOMETA label.

Please let me know if you have any questions.

Thank you

*Modupe O. Fagbami*  
*RPM*  
*Division of Oncology Products 1*  
*Office of Hematology and Oncology Products*  
*CDER, FDA*  
*10903 New Hampshire Avenue*  
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MODUPE O FAGBAMI  
08/23/2012

**From:** Fagbami, Modupe  
**Sent:** Wednesday, August 22, 2012 2:32 PM  
**To:** 'Santoro, Amanda C'  
**Subject:** NDA 204016 Zoledronic Acid Additional Micro Information Request  
**Importance:** High

Hi Amanda,

Please the following Microbiology information request for your response on or before COB, Wednesday, August 29, 2012.

1. What is the [REDACTED] (b) (4)  
at the Grifols facility where the Zoledronic Acid drug product will be filled?  
What are the [REDACTED] (b) (4)  
[REDACTED] the Zoledronic Acid drug product?

Please let me know if you have any questions.

Thank you.

Thanks

*Modupe O. Fagbami*

*RPM*

*Division of Oncology Products 1*

*Office of Hematology and Oncology Products*

*CDER, FDA*

*10903 New Hampshire Avenue*

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MODUPE O FAGBAMI  
08/23/2012

**From:** [Mesmer, Deborah](#)  
**To:** ["Santoro, Amanda C"](#)  
**Subject:** NDA 204016  
**Date:** Monday, August 13, 2012 4:11:13 PM

---

Dear Mr. Santoro,

Please refer to NDA 204016 for Zoledronic Acid Injection, 4 mg/100 mL.

The review team has the following response to your email request to Deborah Mesmer dated August 9, 2012, proposing an amendment for a change to the primary container for the subject drug product.

We remind you that the application is expected to be complete upon submission.

The proposed amendment will be reviewed if resources allow. We recommend that you submit your proposed amendment as soon as possible.

Sincerely,

Debbie Mesmer

**Deborah Mesmer**  
Regulatory Project Manager for Quality  
Office of New Drug Quality Assessment (ONDQA)  
Division of New Drug Quality Assessment (DNDQA1)  
Food and Drug Administration  
White Oak Building 21, Rm 1627  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
(301) 796-4023  
[deborah.mesmer@fda.hhs.gov](mailto:deborah.mesmer@fda.hhs.gov)

---

**From:** Santoro, Amanda C [<mailto:Amanda.Santoro@hospira.com>]  
**Sent:** Thursday, August 09, 2012 10:56 AM  
**To:** Mesmer, Deborah  
**Subject:**

Dear Ms. Mesmer,

This is to inform you of Hospira's intention to file a minor amendment to NDA 204-016, Zoledronic Acid Injection, 4 mg/100 mL.

This minor amendment provides for a change to the primary container for the subject drug product. This includes a minor dimension change to the tubing of the (b) (4) bag to improve the container manufacturing process. The material of the tubing remains identical to that

previously submitted. This amendment will include updates to 2 CTD sections (3.2.P.2.5 and 3.2.P.7), a Certificate of Analysis for the new container, and 1 report to provide the updated microbiological closure integrity challenge study.

Please confirm that per 21 CFR 314.60(b)(3) the filing of this minor amendment will not extend the initial review cycle and will not impact the assigned PDUFA date of November 30, 2012.

Best regards,  
Amanda Santoro

*Amanda Santoro*

Senior Associate  
Global Regulatory Affairs  
Hospira Inc.  
Dept. 389, Building H2  
Lake Forest, IL 60045-5045  
Phone: 224-212-5040 Fax: 224-212-5401  
[Amanda.Santoro@hospira.com](mailto:Amanda.Santoro@hospira.com)

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DEBORAH M MESMER  
08/13/2012

NALLAPERUM CHIDAMBARAM  
08/13/2012

**From:** Fagbami, Modupe  
**Sent:** Monday, July 23, 2012 10:53 AM  
**To:** 'Santoro, Amanda C'  
**Subject:** NDA 204016 Zoledronic Acid DMEPA Information Request  
**Importance:** High

Dear Amanda,

Please find the following information request for your response on or before close of business on Monday, July 30, 2012.

**Information Request for data to support the proposed administration of renally-adjusted doses**

DMEPA is concerned that your proposal for administration of renally-adjusted doses introduces a new practice into the medication use system and places patients at risk for having the entire contents of the bag infused. Specifically, you recommend the user to infuse the specified volume, which is less than the labeled total volume, from the intravenous bag using a volumetric infusion pump. Therefore, we request the following to address our concerns:

1. Discuss whether your proposal to infuse a specific volume, which is less than the labeled total volume, introduces a new practice into the medication use system considering the various medication use processes, facilities, and end-users (physicians, pharmacists, nurses) that will interact with Zoledronic Acid Injection.
2. Are the pumps capable of delivering the exact volume [REDACTED] (b) (4) of the Zoledronic Acid solution? Provide data about the accuracy of drug solution delivery using volumetric pumps that would be used to deliver Zoledronic Acid Injection. What is the error rate (incorrect volume infused) reported with any infusion pump which may be used to infuse this product?
2. Provide data to support the various types of facilities (for example, community hospital, tertiary care center, outpatient oncology practice, comprehensive cancer center) that will likely use Zoledronic Acid Injection actually possess infusion pumps capable of safely administering the specific volume indicated for renally adjusted doses.

Kindly acknowledge receipt of this request and let me know if you have any questions.

Thank you

*Modupe O. Fagbami*

*RPM*

*Division of Oncology Products 1*

*Office of Hematology and Oncology Products*

*CDER, FDA*

*10903 New Hampshire Avenue*

*WO-22, Room 2108*

*Silver Spring, Maryland 20993*

*Phone: 301-796-1348*

*Fax: 301-796-9845*

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MODUPE O FAGBAMI  
07/23/2012

**From:** Fagbami, Modupe  
**Sent:** Monday, July 09, 2012 1:35 PM  
**To:** 'amanda.santoro@hospira.com'  
**Subject:** NDA 204016 Zoledronic Acid CMC Microbiology Information Request  
**Importance:** High

Dear Amanda,

Please find the following CMC Microbiology Information Request for your response on or before Monday, July 23, 2012

1. Please provide a copy (in English) of protocol (b) (4) to include the location if the biological indicators within the load.
2. For the endotoxin assay validation;
  - a. What is the pH of the (b) (4) drug product mix?
  - b. Will the pH of the (b) (4) drug product mix be determined for each assay?
  - c. Please provide the percent recoveries of the product positive controls obtained for the (b) (4) product dilution studies.
3. How is the (b) (4) being controlled? Is it strictly a (b) (4) ?

Kindly let me know if you have any questions.

Thank you

*Modupe O. Fagbami*  
*RPM*  
*Division of Oncology Products 1*  
*Office of Hematology and Oncology Products*  
*CDER, FDA*  
*10903 New Hampshire Avenue*  
*WO-22, Room 2108*  
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MODUPE O FAGBAMI  
07/10/2012

**From:** Fagbami, Modupe  
**Sent:** Thursday, July 05, 2012 12:14 PM  
**To:** 'amanda.santoro@hospira.com'  
**Subject:** NDA 204016 Zoledronic Acid DMEPA Information Request  
**Importance:** High

Dear Amanda,

Please find the following DMEPA Information Request for your response by COB, Friday, July 13, 2012.

DMEPA requests the Applicant submit a replica sample of Zoledronic Acid (carton and (b) (4) ).

Kindly let me know if you have any questions.

Thank you

*Modupe O. Fagbami*  
*RPM*  
*Division of Oncology Products 1*  
*Office of Hematology and Oncology Products*  
*CDER, FDA*  
*10903 New Hampshire Avenue*  
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MODUPE O FAGBAMI  
07/05/2012

**From:** Mesmer, Deborah  
**To:** ["Santoro, Amanda C"](#)  
**Subject:** NDA 204016 Information Request  
**Date:** Friday, June 22, 2012 2:25:00 PM

---

Dear Ms. Santoro,

We refer to NDA 204016 for Zoledronic Acid Injection, 4mg/100 mL.

We have the following comments and requests:

1. Based on batch results and stability data, any unknown impurities in Zoledronic Acid Injection (4mg/100 mL) were not detected. The acceptance criteria for impurity of Any Single Unknown and Total in the drug product specifications uses unconventional terminology. The terms should be revised to specified/unspecified or identified/unidentified impurity, or specified degradation or unidentified degradation products. Refer to ICH 3A and ICH Q3B(R2).
2. **Revise the drug product storage statement as follows:**

(b) (4)

Please submit your response to your application and provide to me a courtesy copy of the submission.

Sincerely,

Deborah Mesmer

**Deborah Mesmer**

Regulatory Project Manager for Quality  
Office of New Drug Quality Assessment (ONDQA)  
Division of New Drug Quality Assessment (DNDQA1)  
Food and Drug Administration  
White Oak Building 21, Rm 1627  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
(301) 796-4023  
[deborah.mesmer@fda.hhs.gov](mailto:deborah.mesmer@fda.hhs.gov)

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DEBORAH M MESMER  
06/22/2012

JANICE T BROWN  
06/25/2012

**From:** [Mesmer, Deborah](#)  
**To:** ["Mohamed, Khaled"](#)  
**Cc:** [Santoro, Amanda C](#)  
**Subject:** RE: NDA 204016 advice  
**Date:** Thursday, May 24, 2012 10:15:00 AM

---

Dear Mr. Mohamed,

We refer to NDA 204016, to the Agency's request for information dated May 17, 2012; to the advice correspondence dated May 22, 2012; and to your further email inquiry dated May 22, 2012, to Deborah Mesmer regarding (b) (4) as a highly potent carcinogen.

We have the following comment:

(b) (4) with known mutagenic activity, and therefore are considered potential carcinogens. If no (b) (4) are detectable in the maximum allowable dose of Zoledronic Acid Injection, then the proposed limit for (b) (4) at NMT (b) (4)% is acceptable.

Please submit your response to your application and provide to me a courtesy copy of the submission.

Sincerely,

Deborah Mesmer

**Deborah Mesmer**  
Regulatory Project Manager for Quality  
Office of New Drug Quality Assessment (ONDQA)  
Division of New Drug Quality Assessment (DNDQA1)  
Food and Drug Administration  
White Oak Building 21, Rm 1627  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
(301) 796-4023  
[deborah.mesmer@fda.hhs.gov](mailto:deborah.mesmer@fda.hhs.gov)

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DEBORAH M MESMER  
05/24/2012

JANICE T BROWN  
05/24/2012

**From:** [Mesmer, Deborah](#)  
**To:** ["Mohamed, Khaled"](#)  
**Cc:** [Santoro, Amanda C](#)  
**Subject:** NDA 204016 advice  
**Date:** Tuesday, May 22, 2012 10:39:00 AM

---

Dear Mr. Mohamed,

We refer to NDA 204016, to the Agency's request for information dated May 17, 2012, and to your email message dated May 18, 2012, to Deborah Mesmer requesting clarification regarding the drug substance specification.

We have the following comment:

According to the recommendation from the pharmacology/toxicology reviewers, (b) (4) is a highly potent carcinogen. The calculated limit should not exceed (b) (4) ppm, which is (b) (4) %.

Please contact me if you have any questions.

Sincerely,

Debbie Mesmer

**Deborah Mesmer**  
Regulatory Project Manager for Quality  
Office of New Drug Quality Assessment (ONDQA)  
Division of New Drug Quality Assessment (DNDQA1)  
Food and Drug Administration  
White Oak Building 21, Rm 1627  
10903 New Hampshire Avenue  
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DEBORAH M MESMER  
05/22/2012

JANICE T BROWN  
05/22/2012

**From:** [Mesmer, Deborah](#)  
**To:** ["khaled.mohamed@hospira.com"](mailto:khaled.mohamed@hospira.com)  
**Subject:** NDA 204016 Information Request  
**Date:** Thursday, May 17, 2012 2:05:00 PM

---

Dear Mr. Khaled,

Please refer to NDA 204016 for Zoledronic Acid Injection. We have the following request. Please submit your response to your application by **May 24, 2012**.

Reduce the level of (b) (4) in the zoledronic acid drug substance specification to NMT (b) (4) ppm.

Please acknowledge receipt of this message, and provide a courtesy copy of your submission to me.

Please let me know if you have any questions.

Sincerely,

Debbie Mesmer

**Deborah Mesmer**  
Regulatory Project Manager for Quality  
Office of New Drug Quality Assessment (ONDQA)  
Division of New Drug Quality Assessment (DNDQA1)  
Food and Drug Administration  
White Oak Building 21, Rm 1627  
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DEBORAH M MESMER  
05/17/2012



NDA 204016

**FILING COMMUNICATION**

Hospira Inc.  
Attention: Khaled M. Mohamed  
Product Manager, Global Regulatory Affairs  
275 North Field Drive  
Dept. 389, Bldg. H2-2  
Lake Forest, IL 60064

Dear Mr. Mohamed:

Please refer to your New Drug Application (NDA) dated January 30, 2012, received January 31, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Zoledronic Acid Injection, 0.04 mg/mL.

We also refer to your amendments dated February 1, 2012, and March 7, 2012.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is **November 30, 2012**.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by **November 2, 2012**.

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

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. There should be no white-space between the 'HIGHLIGHTS OF PRESCRIBING INFORMATION' and the Highlights Limitation Statement.

2. The drug product title must be bolded and in all upper case letters.
3. Only “adverse reactions” should be included in the PI. Avoid using terms, such as “adverse events”. Please ensure this is corrected in the entire label.
4. Format sentence “to report SUSPECTED ADVERSE REACTION” in Highlights (HL).
5. Avoid using terms, such as “rare” and “very rare”. Remove them and re-word the label as appropriate.
6. The subtitle heading for ‘Adverse Reactions’, 6.1, should read, “Clinical Trials Experience”; not “Clinical Studies Experience” as presently stated
7. You should change “postapproval” to “post-approval” in Postmarketing Experience.
8. You should update the proposed PI for NDA 204016 by referencing and incorporating (as appropriate) the most recently approved RLD’s PI.
9. You should remove the revision date on the last page since it is already in Highlights (HL).

We request that you resubmit labeling that addresses these issues by May 3, 2012. The resubmitted labeling will be used for further labeling discussions.

### **PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide, and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

**REQUIRED PEDIATRIC ASSESSMENTS**

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

Because none of these criteria apply to your application, you are exempt from this requirement

If you have any questions, call Modupe Fagbami, Regulatory Project Manager, at (301) 796-1348.

Sincerely,

*{See appended electronic signature page}*

Amna Ibrahim, M.D.  
Deputy Director  
Division of Oncology Products 1  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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AMNA IBRAHIM  
04/12/2012



NDA 204016

**NDA ACKNOWLEDGMENT**

Hospira Inc.  
Attention: Khaled M. Mohamed  
Product Manager, Global Regulatory Affairs  
275 North Field Drive  
Dept. 389, Bldg. H2-2  
Lake Forest, IL 60064

Dear Mr. Mohamed:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Zoledronic Acid Injection, 0.04 mg/mL

Date of Application: January 30, 2012

Date of Receipt: January 31, 2012

Our Reference Number: NDA 204016

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 March 31, 2012, in accordance with 21 CFR 314.101(a).

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

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory

registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 204016** submitted on **January 30, 2012**, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

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

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Oncology Products 1  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, call me at (301) 796-1348.

Sincerely,

*{See appended electronic signature page}*

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MODUPE O FAGBAMI  
02/13/2012

## Pre-IND/ Pre- NDA Meeting: IND 113457

Sponsor: Hospira Inc.

Drug: zoledronic acid Injection, 0.04mg/mL

### Sponsor Questions with FDA Responses

**Background:** Hospira proposes to submit a 505(b)(2) application for a (b)(4) 4 mg formulation of zoledronic acid. The proposed indications are the same as for the Reference Listed Drug (RLD) Zometa®:

- Hypercalcemia of malignancy
- Treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumor

The following table provides a comparison of the RDL and the generic equivalent.

		Reference Listed Drug	Generic Equivalent
Active Ingredient(s)		Zoledronic Acid (4 mg)	Zoledronic Acid (4 mg)
Inactive Ingredient(s)		Mannitol, USP (220 mg) Sodium Citrate, USP (24 mg) Water for Injection, USP	Mannitol, USP (220 mg) Sodium Citrate, USP (24 mg) Sodium Chloride, USP (900 mg) Water for Injection, USP
Strength	Concentrate	4 mg/5 mL (0.8 mg/mL)	Not applicable
	Post Dilution*	4 mg/100mL (0.04 mg/mL)	4 mg/100 mL (0.04 mg/mL)
Diluents		100 mL 5% Dextrose Or 100 mL 0.9% Sodium Chloride	Not applicable

\* Per Dosage and Administration guidance in RLD Label

The conditions of use (indications), dosage form, concentration, strength, route of administration, quantitative and qualitative composition of the active and inactive ingredients for the proposed Hospira drug product, Zoledronic Acid Injection 4 mg/100 mL (b)(4) recommended for use in the RLD, (b)(4) 100 mL of 0.9% sodium chloride. Hospira's formulation does not introduce new ingredients or result in a deviation from dosage form, dosing regimen or route of administration. Thus, the basis of this application and its approval upon review is supported by the safety and efficacy findings of the RLD. As a result the sponsor has requested a waiver for performance of *in vivo* bioavailability / bioequivalence requests and a waiver for the requirement to perform pediatric studies.

- A. Hospira developed a (b)(4) formulation comparable to the approved Zometa (zoledronic acid) Injection 4 mg/5mL concentrate (NDA 021-223) upon dilution with 0.9% sodium chloride. Hospira intends to file a 505(b)(2) New Drug Application referencing the Zometa concentrate. Is the filing pathway and proposed RLD acceptable to the Agency?

**FDA Response:**

A 505(b)(2) application would be an acceptable approach at this time based on the information provided. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>)

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate. We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature.

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which we consider to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that is the subject of an NDA approved under section 505(c) of the FD&C Act.

**The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.**

**Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a duplicate of that drug and eligible for approval under section 505(j) of the FD&C Act, we may refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an ANDA that cites the duplicate product as the reference listed drug.**

- B. Hospira intends to request a waiver of the in-vivo Bioavailability or Bioequivalence based on the proposed product formulation and intended use. Is the waiver strategy acceptable to the Agency?**

**FDA Response:**

**Yes, the provided biowaiver strategy is acceptable. A waiver from the requirement to conduct an in vivo bioavailability or bioequivalence study should be requested for Zoledronic Acid Injection (0.04 mg/mL) at the time of the NDA submission.**

- C. Hospira intends to request a waiver for pediatric study evaluation for the proposed drug product, because the subject formulation does not introduce new ingredients, indications, or a change in dosage form, regimen, and/or route of administration from the currently approved RLD. Is the waiver strategy acceptable to the Agency?**

**FDA Response:**

**We are unable to answer your question at this time. Please submit a request for a waiver at the time of the NDA submission.**

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