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

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

\[ \text{YES} \quad \text{NO} \]

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?

\[ \text{YES} \quad \text{NO} \]

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?

\[ \text{YES} \quad \text{NO} \]

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.

\[ \text{YES} \quad \text{NO} \]

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

Investigation #1

Investigation #2

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

Investigation #2
If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

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

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

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

Investigation #1

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Investigation #2

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(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?
Investigation #1

YES ☐ 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:

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

/s/

JEANNETTE L O'DONNELL
12/28/2015

GEOFFREY S KIM
12/28/2015
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
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)(l) 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

<table>
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<tr>
<th>NDA #</th>
<th>NDA Supplement #</th>
<th>BLA #</th>
<th>BLA Supplement #</th>
<th>If NDA, Efficacy Supplement Type: (an action package is not required for SE8 or SE9 supplements)</th>
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Proprietary Name: Established/Proper Name: Zoledronic Acid Solution
Dosage Form: Intravenous Infusion

RPM: Jeannette O’Donnell
Division: Oncology Products 1

Applicant: Hospira, Inc.
Agent for Applicant (if applicable):

NDA Application Type: □ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: □ 505(b)(1) □ 505(b)(2)

BLA Application Type: □ 351(k) □ 351(a)
Efficacy Supplement: □ 351(k) □ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- Review the information in the 505(b)(2) Assessment and submit the draft\(^2\) to CDER OND IO for clearance.
- Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)
  
□ No changes
□ New patent/exclusivity *(notify CDER OND IO)*

Date of check: 12/7/15

**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.

### Actions

- Proposed action
- User Fee Goal Date is 1/2/16

- Previous actions (specify type and date for each action taken)

- 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 [http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf)). If not submitted, explain

- Received

### Application Characteristics

1 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.

2 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).

3 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.

Reference ID: 3866896

Version: 11/20/15
Review priority:  □ Standard  □ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☐ Fast Track  ☐ Rx-to-OTC full switch
☐ Rolling Review  ☐ Rx-to-OTC partial switch
☐ Orphan drug designation  ☐ Direct-to-OTC
☐ 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)
  ☐ Approval based on animal studies

BLAs: Subpart E  ☐ Accelerated approval (21 CFR 601.41)
  ☐ Restricted distribution (21 CFR 601.42)
  ☐ Approval based on animal studies

REMSS: ☐ 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 (approvals only)  □ Yes  □ No
- Public communications (approvals only)
  - Office of Executive Programs (OEP) liaison has been notified of action  □ Yes  □ No
  - Indicate what types (if any) of information were issued
- Exclusivity
  - Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?  □ No  □ 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.
      - □ Verified
      - □ Not applicable because drug is an old antibiotic

**CONTENTS OF ACTION PACKAGE**

**Officer/Employee List**
- List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)  □ Included
- Documentation of consent/non-consent by officers/employees  □ Included

Reference ID: 3866896
### 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

---

### 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)*
    - Included
  - Original applicant-proposed labeling
    - Included
  - Medication Guide
    - Patient Package Insert
    - Instructions for Use
    - None

- **Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling** *(write submission/communication date at upper right of first page of each piece)*
  - Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*
    - Included
  - Original applicant-proposed labeling
    - 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
    - Included

- **Proprietary Name**
  - Acceptability/non-acceptability letter(s) *(indicate date(s))*
  - Review(s) *(indicate date(s))*
  - Not Applicable – No proprietary name requested

- **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

### Administrative / Regulatory Documents

- **RPM Filing Review**/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
  - Not a (b)(2) 12/8/15

- **NDAs only: Exclusivity Summary** *(signed by Division Director)*
  - 12/28/15

- **Application Integrity Policy (AIP) Status and Related Documents**
  - [http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm](http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm)
  - Applicant is on the AIP
    - Yes

---

4 Filing reviews for scientific disciplines are NOT required to be included in the action package.
- This application is on the AIP
  - If yes, Center Director’s Exception for Review memo *(indicate date)*
  - If yes, OC clearance for approval *(indicate date of clearance communication)*
    - [ ] Yes  [x] No
    - [ ] Not an AP action

- Pediatrics *(approvals only)*
  - Date reviewed by PeRC _______
    - If PeRC review not necessary, explain: 505(b)(2) that does not need PeRC

- Breakthrough Therapy Designation
  - [ ] N/A

- Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)

- CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*

- CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)*
  - *(completed CDER MPC templates can be found in DAARRTS as clinical reviews or on the MPC SharePoint Site)*

- 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.) *(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)*

- 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
  - If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*  [x] N/A or no mtg
  - Pre-NDA/BLA meeting *(indicate date of mtg)*  [x] No mtg 1/2/2012
  - EOP2 meeting *(indicate date of mtg)*  [x] No mtg
  - Mid-cycle Communication *(indicate date of mtg)*  [x] N/A
  - Late-cycle Meeting *(indicate date of mtg)*  [x] N/A
  - Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) Teleconferences
    - 9/10/12, 2/6/13, and 6/3/13

- Advisory Committee Meeting(s)
  - [x] No AC meeting

- Date(s) of Meeting(s)

### Decisional and Summary Memos

- Office Director Decisional Memo *(indicate date for each review)*  [x] None
  - Division Director Summary Review *(indicate date for each review)*  [x] None 7/3/13, 11/29/12, 12/28/15
  - Cross-Discipline Team Leader Review *(indicate date for each review)*  [x] None 7/3/13, 11/15/12
  - PMR/PMC Development Templates *(indicate total number)*  [x] None

#### Clinical
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<td>Financial Disclosure reviews(s) or location/date if addressed in another review OR</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Environmental Assessment (check one) (original and supplemental applications)</td>
<td></td>
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<tr>
<td>☒ Categorical Exclusion (indicate review date) (all original applications and all efficacy supplements that could increase the patient population) 10/11/12</td>
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<td>☐ Review &amp; FONSI (indicate date of review)</td>
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<td>☐ Review &amp; Environmental Impact Statement (indicate date of each review)</td>
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<tr>
<td>Facilities Review/Inspection</td>
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<td>☐ Acceptable Re-evaluation date:</td>
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<tr>
<td>☐ Withhold recommendation</td>
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</tr>
<tr>
<td>☐ Not applicable</td>
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</tr>
</tbody>
</table>

Reference ID: 3866896
### Day of Approval Activities

<table>
<thead>
<tr>
<th>For all 505(b)(2) applications:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</td>
</tr>
<tr>
<td>- Finalize 505(b)(2) assessment</td>
</tr>
<tr>
<td>- For Breakthrough Therapy (BT) Designated drugs:</td>
</tr>
<tr>
<td>- Notify the CDER BT Program Manager</td>
</tr>
<tr>
<td>- For products that need to be added to the flush list (generally opioids): Flush List</td>
</tr>
<tr>
<td>- Notify the Division of Online Communications, Office of Communications</td>
</tr>
<tr>
<td>- Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email</td>
</tr>
<tr>
<td>- If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter</td>
</tr>
<tr>
<td>- Ensure that proprietary name, if any, and established name are listed in the Application Product Names section of DARRTS, and that the proprietary name is identified as the “preferred” name</td>
</tr>
<tr>
<td>- Ensure Pediatric Record is accurate</td>
</tr>
<tr>
<td>- Send approval email within one business day to CDER-APPROVALS</td>
</tr>
</tbody>
</table>

- No changes
- New patent/exclusivity (Notify CDER OND IO)
- Done
- Send email to CDER OND IO
- Not applicable
- Done
- Not applicable
- Done
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/s/

JEANNETTE L O’DONNELL
12/30/2015
I saw one more thing that needs to be addressed. The C/C label states [REDACTED]. We have very stringent requirements for this claim (please see attached). Xing/Xiao-Hong, let’s get together about this later today.

Olen

Hi All,

As chemistry was the only division to request a change [REDACTED] 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
Folks,

Here is the bottom line on the issue with regards to labeling in ONDQA reviews and advice to sponsors and applicants. First, ONDQA does not recommend to allow 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 ) regarding natural rubber latex or variant related terms such as . 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 unsupportable claim that the medical product is of or 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 or in medical product labeling should update their medical product labeling to show the recommended labeling statement “Not made with natural rubber latex” or “The is not made with natural rubber latex” as appropriate. Alternatively, manufacturers should consider removing 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: 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: please see below
Hi 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

Reference ID: 3863564
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

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
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:

- Internal Talking Points distributed to OPA and DSMICA
- Notify industry via CDRH Twitter
- Announced in CDRH New
- Targeted outreach to industry: e-mail/call to AVAMED and Medical Device Manufacturer Association
- Announced in OSHI Patient and Health Care Newsletters
- 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

Phone: 301-796-5854

Email: janesia.simmons@fda.hhs.gov

Website: www.fda.gov

Reference ID: 3863564
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/s/

JEANNETTE L O’DONNELL
12/21/2015
archiving CMC comments

Reference ID: 3863564
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) Revise the Prescribing Information (PI) labeling and container labeling to change the term (b)(4) to “not made with natural rubber latex” or remove the (b)(4) 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
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/s/

----------------------------------------------------
JEANNETTE L O'DONNELL
12/17/2015
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
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/s/

JEANNETTE L O’DONNELL
12/14/2015
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

Dear Ms. Santoro,

After reviewing all of the labeling including container, carton, and PI for this product, I noticed that the container label also contains the phrase “Only – Discard Unused Portion.” Accordingly, can I assume that the request below should also be applied to the container label?

Kind regards,
Amanda

Dear Ms. Santoro,

O’Donnell, Jeannette
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 [redacted] 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

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/s/

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.

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/

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.

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

Reference ID: 3848350
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/s/

JEANNETTE L O'DONNELL
11/18/2015
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

---

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
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

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
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/

MODUPE O FAGBAMI
06/18/2013
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). 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.2

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)3 with respect to

---

1 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.


3 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)).

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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4 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.”

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 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.

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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5 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.

6 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.

7 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.8

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

---

8 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:

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

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 such changes to formulations that take it out of the 505(j) process.

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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9 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.

10 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 that is not present in the 4 mg/5 mL presentation of Zometa. Mannitol and the admixture are not considered exception excipients and therefore submission of an ANDA would not have been permitted.

11 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., 505(b)(2)(NDA)), that did not certify to the ‘241 patent. Contrary to Hospira’s assumption, 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/

MODUPE O FAGBAMI
06/03/2013

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

ROBERT L JUSTICE
06/03/2013
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). 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

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1 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\(^2\) 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.\(^3\)

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).\(^4\)

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

\(^2\) 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.

\(^3\) Compare 21 C.F.R. 314.54(b) (describing situations in which a 505(b)(2) application may not be submitted).

\(^4\) 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.5

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., Hospira (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.

5 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
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT L JUSTICE
06/03/2013
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/

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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/s/

MODUPE O FAGBAMI
02/12/2013

ALI H AL HAKIM
02/12/2013
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

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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 site 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

CONFIDENTIALITY STATEMENT. This email and any attachment is for the sole use of the intended recipient and may contain private, confidential and/or privileged information that may be subject to Hospira internal policies. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you have received this transmission in error, please notify Hospira immediately by return email or by email.
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/s/

MODUPE O FAGBAMI
02/04/2013
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/

MODUPE O FAGBAMI
01/29/2013

Reference ID: 3252292
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.

Kindly let me know if you have any questions.

Thank you

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

MODUPE O FAGBAMI
11/15/2012
Fagbami, Modupe

From: Liu, Qi (CDER)
Sent: Wednesday, November 14, 2012 9:50 AM
To: 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.
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
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Silver Spring, Maryland 20993
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Fax: 301-796-9845
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/s/

MODUPE O FAGBAMI
10/15/2012
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

---

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
Office of Hematology and Oncology Products
CDER, FDA
10903 New Hampshire Avenue
WO-22, Room 2108
Silver Spring, Maryland 20993
Phone: 301-796-1348
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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] publications and there is an estimated [redacted] market for [redacted], 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 you proposal, we request the following:

1. Improve the description of the transfer device. The term [redacted] that is used in section 2.3 of the package insert labeling is ambiguous and does not clearly define the intend device. Specify the transfer device, commercial availability, material of construction (e.g., [redacted]), 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] bag for withdrawal of solution during preparation and administration to the patient.

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/s/

LISA M SKARUPA
09/24/2012
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*
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/s/

________________________________________
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. 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 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 (3)(6)
- 3.3 mg (3)(6)
- 3 mg (3)(6)

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. 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 (3)(6) 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

Modupe Fagbami, RPM, DOP1/IOHOP          Haripada Sarker, Ph.D., CMC Lead, DNDQA I/ONDQA
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/s/

MODUPE O FAGBAMI
11/16/2012

HARIPADA SARKER
11/16/2012
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. 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 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/100 mL
   3.3 mg/100 mL
   3 mg/100 mL

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  
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/

MODUPE O FAGBAMI
09/05/2012
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)
         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)
      c. Delete the statement, (b) (4)
   4. Revise the statement, (b) (4) to read as follows:
      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:
      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:
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
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/s/

MODUPE O FAGBAMI
08/28/2012
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 bag. Please respond to the following information request by noon EST on 8/24:

1. Container-closure:

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

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
WO-22, Room 2108

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/s/

MODUPE O FAGBAMI
08/23/2012
Hi Amanda,

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

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

*Office of Hematology and Oncology Products*

*CDER, FDA*

*10903 New Hampshire Avenue*

*WO-22, Room 2108*

*Silver Spring, Maryland 20993*

*Phone: 301-796-1348*

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/s/

MODUPE O FAGBAMI
08/23/2012
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 (DNDQA)
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

---

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 [0/4] 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

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/s/

DEBORAH M MESMER
08/13/2012

NALLAPERUM CHIDAMBARAM
08/13/2012
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 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  
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/s/

MODUPE O FAGBAMI
07/23/2012
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
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/s/

MODUPE O FAGBAMI
07/10/2012
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
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/s/

MODUPE O FAGBAMİ
07/05/2012

Reference ID: 3154800
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:

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  
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deborah.mesmer@fda.hhs.gov

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DEBORAH M MESMER
06/22/2012

JANICE T BROWN
06/25/2012
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 as a highly potent carcinogen.

We have the following comment:

If no are detectable in the maximum allowable dose of Zoledronic Acid Injection, then the proposed limit for at NMT % 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
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deborah.mesmer@fda.hhs.gov

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/s/

DEBORAH M MESMER
05/24/2012

JANICE T BROWN
05/24/2012
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, (6)(b)(6) is a highly potent carcinogen. The calculated limit should not exceed (6)(b)(6) ppm, which is (6)(b)(6)%.

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)
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(301) 796-4023
deborah.mesmer@fda.hhs.gov

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/s/

DEBORAH M MESMER
05/22/2012

JANICE T BROWN
05/22/2012
Dear Mr. Khaled,

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

Reduce the level of $(8(4))$ in the zoledronic acid drug substance specification to NMT $(6(4))$ 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  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
(301) 796-4023  
deborah.mesmer@fda.hhs.gov
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/s/

DEBORAH M MESMER
05/17/2012
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](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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/s/

AMNA IBRAHIM
04/12/2012
NDA 204016

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/FederalFoodDrugandCosmeticActFDCA ct/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}

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

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 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.

<table>
<thead>
<tr>
<th>Active Ingredient(s)</th>
<th>Reference Listed Drug</th>
<th>Generic Equivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoledronic Acid (4 mg)</td>
<td>Mamitol, USP (220 mg)</td>
<td>Mamitol, USP (220 mg)</td>
</tr>
<tr>
<td>Sodium Citrate, USP (24 mg)</td>
<td>Sodium Citrate, USP (24 mg)</td>
<td></td>
</tr>
<tr>
<td>Water for Injection, USP</td>
<td>Sodium Chloride, USP (900 mg)</td>
<td>Water for Injection, USP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Strength</th>
<th>Concentrate</th>
<th>Post Dilution*</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 mg/5 mL (0.8 mg/mL)</td>
<td>4 mg/100mL (0.04 mg/mL)</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

* 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, are recommended for use in the RLD, 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 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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MODUPE O FABGAMI
01/12/2012