

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204016Orig1s000**

**MICROBIOLOGY/VIROLOGY REVIEW(S)**

# Product Quality Microbiology Review

04 October 2012

**NDA:** 204-016/N-000

**Drug Product Name**

**Proprietary:** N/A

**Non-proprietary:** Zoledronic Acid Injection, 0.04mg/ml

**Review Number:** 1

**Dates of Submission(s) Covered by this Review**

<b>Submit</b>	<b>Received</b>	<b>Review Request</b>	<b>Assigned to Reviewer</b>
30 January 2012	31 January 2012	28 February 2012	29 February 2012
30 April 2012	30 April 2012	n/a	n/a
23 July 2012	23 July 2012	n/a	n/a
14 August 2012	14 August 2012	n/a	n/a

**Submission History (for amendments only):** N/A

**Applicant/Sponsor**

**Name:** Hospira, Inc.

**Address:** 275 North Field Dr.  
Dept. 0389, Bldg. H2-2  
Lake Forest, IL 60045

**Representative:** Khaled M Mohamed  
Product Manager Regulatory Affairs

**Telephone:** 224-212-4909

**Name of Reviewer:** Robert J. Mello, Ph.D.

**Conclusion:** The application is recommended for approval from microbiology product quality standpoint.

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## Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** 505(b)(2)
  2. **SUBMISSION PROVIDES FOR:** Marketing authorization
  3. **MANUFACTURING SITE:**  
Laboratorios Grifols, S.A.  
(b) (4)  
[REDACTED]  
[REDACTED]  
[REDACTED] arcelona, Spain  
FEI# 3002807257
  4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Sterile solution, Intravenous injection, 4mg/100ml (0.04 mg/ml) packaged in a single port, 100ml (b) (4) intravenous infusion.
  5. **METHOD(S) OF STERILIZATION:** (b) (4)
  6. **PHARMACOLOGICAL CATEGORY:** Treatment of hypercalcemia of malignancy and for treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors.
- B. **SUPPORTING/RELATED DOCUMENTS:** None
- C. **REMARKS:**
- The submission was provided in eCTD format and was available for review in EDR.
  - An ONDQA filing review was submitted on 09 March 2012. No specific questions were referred to OPS/NDMS. This reviewer's Filing Review was entered into DARRTS on 08 March 2012.
    1. On 09 July 2012, a Microbiology Information Request was transmitted to the Applicant by the Project Manager. The Applicant replied to the information request on 23 July 2012. Those responses are incorporated into the body of this review.

**Filename:** N204016N000R1.doc

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**Executive Summary**

**I. Recommendations**

- A. Recommendation on Approvability - Recommend Approval**
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable - Not Applicable**

**II. Summary of Microbiology Assessments**

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology - The drug product is formulated and** <sup>(b) (4)</sup>  

- B. Brief Description of Microbiology Deficiencies - None**
- C. Assessment of Risk Due to Microbiology Deficiencies - N/A**

**III. Administrative**

- A. Reviewer's Signature:** \_\_\_\_\_  
Robert J. Mello, Ph.D.  
Senior Microbiology Reviewer
- B. Endorsement Block:** \_\_\_\_\_  
John W. Metcalfe, Ph.D.  
Senior Microbiology Reviewer
- C. CC Block**  
NDA 204016

**Product Quality Microbiology Assessment**

**1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q)  
MODULE 3.2: BODY OF DATA**

**S DRUG SUBSTANCE:** The drug substance is not sterile.

**P DRUG PRODUCT**

**P.1 Description of the Composition of the Drug Product**

- Description of drug product – Zoledronic acid, 4 mg/100 mL, is a sterile aqueous solution for intravenous infusion.
- Drug product composition – The composition of the drug product is provided below (copied from submission Section 3.2.P.1, Table 2, page 2/2):

**Table 2. Quantitative Composition**

Component	Quantity per Milliliter (mL)	Strength: 4 mg/100mL
		Quantity per unit
Zoledronic Acid	0.04 mg <sup>1</sup>	4.0 mg <sup>1</sup>
Mannitol	2.2 mg	220 mg
Sodium Citrate	0.24 mg <sup>1</sup>	24 mg <sup>1</sup>
Sodium Chloride	9.0 mg	900 mg
Water for Injection	q.s. to 1 mL	q.s. to 100 mL
Total Volume	1.00 mL	100 mL

q.s. = Quantity sufficient  
1 Theoretical amount on an anhydrous basis

- Description of container closure system – The container closure system consists of a 100 mL (b) (4) bag (b) (4)

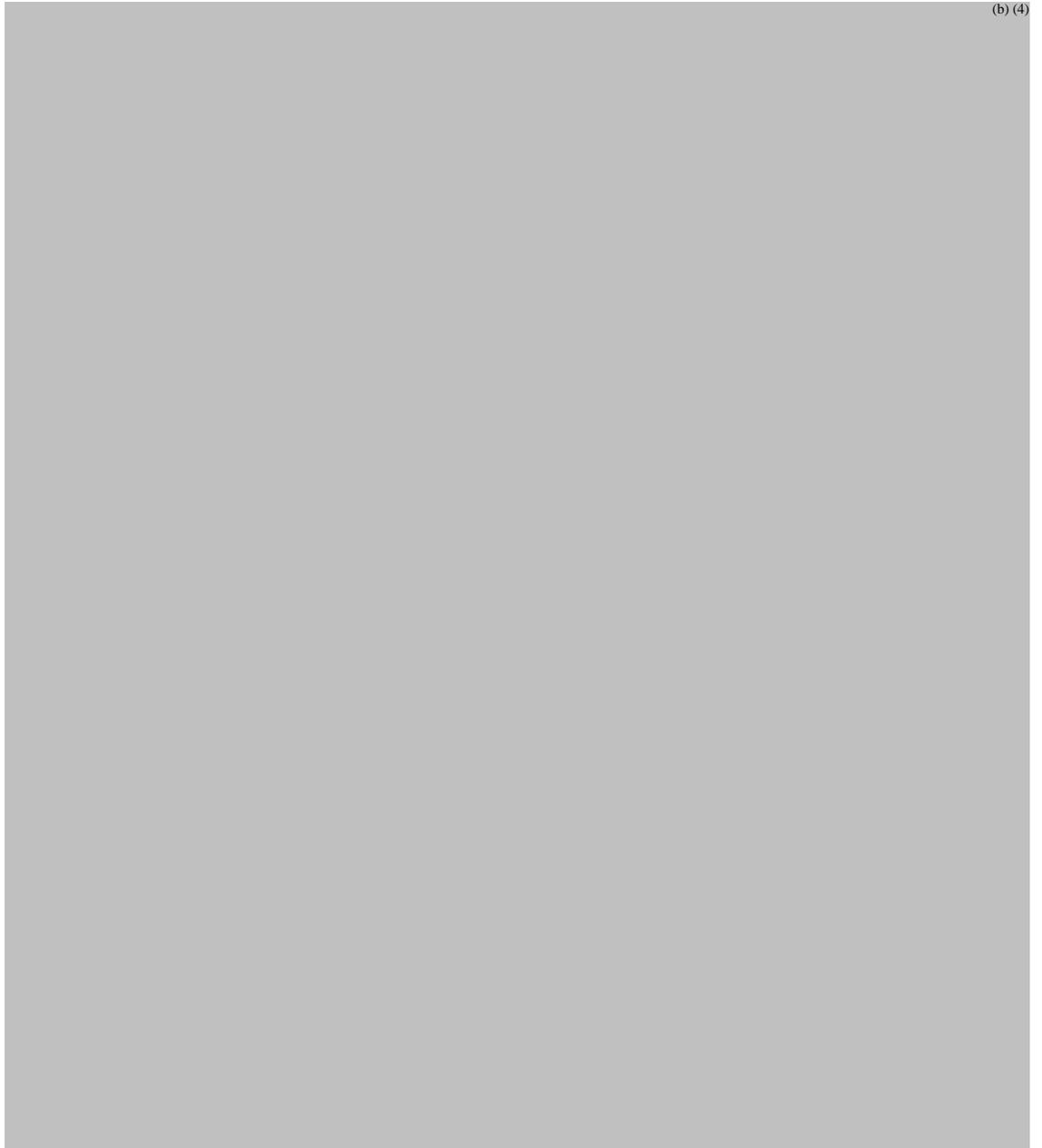
twist-off cap. The bags are (b) (4)

(b) (4)

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**P.2 Pharmaceutical Development****P.2.5 Microbiological Attributes:**

- Container-Closure and Package Integrity (CCI) - On 14 August 2012, the applicant submitted an amendment for a minor change in the port tube dimensions. This would not affect (b) (4) but the container-closure testing would be affected. The applicant submitted updated test results (see below) using the new tube. (Note: the only changes in the tubing were fractional increases in dimension. (b) (4) processes were unchanged.)



- Justification for not having a microbial limit specification for a non-sterile drug product - The drug product is sterile.

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/s/  
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ROBERT J MELLO  
10/04/2012

JOHN W METCALFE  
10/04/2012  
I concur.

# PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 204-016

Applicant: Hospira, Inc.

Letter Date: 30 January 2012

Drug Name: Zoledronic Acid Injection, 0.04mg/ml  
NDA Type: 505(b)(2)

Stamp Date: 31 January 2012

The following are necessary to initiate a review of the NDA application:

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	X		
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		Module 3, Section 3.2.P.3.3
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	X		Module 3, Section 3.2.P.3.5
4	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		X	
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?	X		Container closure testing: Module 3, Section 3.2.P.2.5. Product is not preserved.
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		Module 3, Section 3.2.P.5.1
7	Has the applicant submitted the results of analytical method verification studies?	X		Module 3, Section 3.2.P.5.3
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?	-	-	Not applicable
9	Is this NDA fileable? If not, then describe why.	X		<b>The NDA is fileable from a microbiology product quality perspective.</b>

**Additional Comments:** The drug product is formulated at 0.04mg/ml and packaged in 100ml (b) (4) bags having one tube with a twist-off administration cap. (b) (4)

3/8/2012

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Robert J. Mello, Ph.D. (Senior Microbiology Reviewer) Date

3/8/2012

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Stephen E. Langille, Ph.D. (Senior Microbiology Reviewer) Date

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/s/  
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ROBERT J MELLO  
03/08/2012

STEPHEN E LANGILLE  
03/08/2012