

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205917Orig1s000**

**MICROBIOLOGY / VIROLOGY REVIEW(S)**

# Product Quality Microbiology Review

18 August 2014

**NDA:** 205-917/N-000

**Drug Product Name**

**Proprietary:** N/A

**Non-proprietary:** paricalcitol injection

**Review Number:** 1

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

Submit	Received	Review Request	Assigned to Reviewer
07 June 2013	10 June 2013	14 June 2013	18 June 2013

**Submission History (for 2<sup>nd</sup> Reviews or higher):** N/A

**Applicant/Sponsor**

**Name:** Hikma Pharmaceuticals Co. Ltd.

**Address:** Industrial Area  
Bayader Wadi El Seer  
Amman  
Jordan

**Representative:** Jonathan E. Sterling, VP Quality,  
Regulatory and Product Development  
Exela Pharma Sciences, LLC.  
1325 William White Place NE  
Lenoir, NC 28645

**Telephone:** 828-757-7888

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

**Conclusion:** Recommended for Approval

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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:** Exela Pharma Sciences  
1325 William White Place  
Lenoir, NC 28645  
FEI#: 3008563008
  - 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Injection, Intravenous, 2mcg/mL and 5mcg/mL packaged in 2mL Type I tubing glass vial with a (b) (4) red flip-off aluminum overseal. The 2mcg/mL presentation is supplied as a 1.0 mL single-dose vial. The 5mcg/mL presentation is supplied as both a 1.0 mL and a 2.0mL single-dose vial.
  - 5. METHOD(S) OF STERILIZATION:** (b) (4)
  - 6. PHARMACOLOGICAL CATEGORY:** Treatment of hyperparathyroidism associated with chronic kidney disease.
- B. SUPPORTING/RELATED DOCUMENTS:**
- LoA from (b) (4) to reference their DMF # (b) (4) for the (b) (4).
  - Microbiology review #24 of DMF (b) (4) dated 2/25/2013 (S. Steffen).
- C. REMARKS:**
- The submission is in CTD format but not in electronic CTD format. It is available in the Electronic Document Room (EDR).
  - The reference listed drug (RLD) is Abbott's ZEMPLAR (Paricalcitol) Injection. However, the Applicant's formulation contains more (b) (4) (35% vs (b) (4)%) than the RLD. It also contains 7% sorbitol (0% in RLD) (b) (4).

**filename:** N205917N000R1

**Executive Summary**

**I. Recommendations**

- A. Recommendation on Approvability - Recommended for Approval**
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable - N/A**

**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> 2mL (13mm) glass vials. The vials are stoppered and secured with aluminum overseals. Sealed units are <sup>(b) (4)</sup>

- B. Brief Description of Microbiology Deficiencies - None**
- C. Assessment of Risk Due to Microbiology Deficiencies – N/A**
- D. Contains Potential Precedent Decision(s)-  Yes  No**

**III. Product Quality Microbiology Risk Assessment**

**A. Initial Product Quality Microbiology Risk Assessment**

CQA	Risk Factor	Prob. of Occ. (O)	Modifier for O <sup>(3,4,5)</sup>	Severity of Effect (S)	Detect. (D)	Risk Priority Number <sup>6</sup> (RPN)	Additional Review Emphasis based on Risk (in addition to normal review process)
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**B. Final Risk Assessment** – The applicant has demonstrated adequate controls over the manufacturing process to mitigate the sterility (b) (4)

[Redacted]

There was also adequate primary container closure integrity study data supporting the sterility maintenance of the final packaged product

**III. Administrative**

**A. Reviewer's Signature** \_\_\_\_\_  
Robert J. Mello, Ph.D.  
Senior Microbiology Reviewer

**B. Endorsement Block** \_\_\_\_\_  
Neal J. Sweeney, Ph.D.  
Senior Microbiology Reviewer

**C. CC Block**  
NDA 205-917

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/s/  
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ROBERT J MELLO  
08/22/2014

NEAL J SWEENEY  
08/22/2014  
I concur.

## PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

**NDA Number:** 205-917

**Applicant:** Hikma  
Pharmaceuticals Co. Ltd.

**Submit Date:** 07 June 2013

**Drug Name:** Paricalcitol  
Injection

**NDA Type:** 505(b)(2)

**Received Date:** 10 June 2013

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		The submission is in CTD format but was not structured in the electronic, eCTD format.
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		Section M3, 3.2.P.3.3. Filename: manuf-process.pdf
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	X		Product is (b) (4) Section M3, 3.2.P.3.5. Filename: product-process-validation.pdf
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 (CCI) studies?	X		Drug product is not preserved. CCI studies used (b) (4) testing. Section M3, 3.2.P.2.5. Filename: microbiological-attributes.pdf
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		Section M3, 3.2.P.5.1 Filename: specifications.pdf
7	Has the applicant submitted the results of analytical method verification studies?	X		Section M3, 3.2.P.5.3 Filename: (b) (4)
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?	-	-	N/A
9	If sterile, are extended post-constitution and/or post-dilution hold times in the draft labeling supported by microbiological data?	-	-	N/A; Product is used immediately
10	Is this NDA fileable? If not, then describe why.	X		

**Additional Comments:** The submission is available for review in EDR but not available for review using Global Submit (non-eCTD format). Paricalcitol Injection, 2 mcg/mL and 5 mcg/mL, will be packaged in 1mL and 2mL glass vials sealed with (b) (4) stoppers. The drug product contains 35% alcohol and 7% sorbitol. It is not preserved and is (b) (4). Dosing is 0.04 mcg/kg to 0.1 mcg/kg (70Kg adult dose of 2.8-7µg) IV bolus. The bulk

drug product is

(b) (4)

**The NDA submission is fileable from a product quality microbiology standpoint.**

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Robert J. Mello, Ph.D.

Senior Review Microbiologist

Date

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John W. Metcalfe, Ph.D.

Senior Review Microbiologist

Date

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/s/  
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ROBERT J MELLO  
06/21/2013

JOHN W METCALFE  
06/21/2013  
I concur.