CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207174Orig1s000

MICROBIOLOGY/VIROLOGY REVIEW(S)

Product Quality Microbiology Review

26 JAN 2015

NDA: 207-174

Drug Product Name
Non-proprietary: Paricalcitol Injection

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
01 APR 2014	01 APR 2014	01 APR 2014	02 APR 2014
20 JUN 2014	20 JUN 2014	N/A	N/A
24 SEP 2014	24 SEP 2014	N/A	N/A
23 JAN 2015	23 JAN 2015	N/A	N/A

Applicant/Sponsor
Name: Accord Healthcare
Address: 1009 Slater Road
Suite 210-B
Durham, NC 27703
Representative: Sabita Nair
Telephone: 919-941-7880

Name of Reviewer: Jessica G. Cole, PhD

Conclusion: Recommended for Approval

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original 505(b)(2) NDA

2. SUBMISSION PROVIDES FOR: New drug product

3. MANUFACTURING SITE:
Intas Pharmaceuticals Ltd
Lot #457, 458
Village: Matoda, Taluka: Sanand, Sarkhej - Bavla Highway
Ahmedabad, Gujarat India
CFN 3003157498

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:

- 2 µg/mL and 5 µg/mL in 1 mL single dose vial and 5 µg/mL in a 2 mL vial multi dose vial
- Intravenous injection
- Preserved solution (35% ethanol)

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Treatment of secondary hyperparathyroidism associated with stage 5 chronic kidney disease

B. SUPPORTING/RELATED DOCUMENTS: None.

C. REMARKS: This submission is in the eCTD format. The following information request was sent to the applicant on 15 September 2014 and a response was received on 24 September 2014.

Microbiology Comment:

Please provide the following information or a reference to its location in the subject submission.

a. Additional information is needed for the antimicrobial effectiveness testing (AET) conducted to support the multiple dose vial. Provide the following:
   a. Justify the conduct of AET at (b) (4)
   b. Justify the conduct of AET on a single batch of the 5 mg/mL formulation. Traditionally, three batches are evaluated.
   c. Summarize the (b) (4) report. We refer to page 208/210 of Module 3.2.P.2.

b. Provide a description of the (b) (4) utilized in routine and validation runs (b) (4).

c. We refer to the (b) (4) validation studies for P-035 and P-036. Provide the following information (b) (4).
   a. Confirm that the biological (b) (4)

b. Provide the [redacted] (b) (4)
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For more information please refer to the following Guidance document(s):
Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products
(http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072171.pdf)

The following information request was sent to the project manager on 06 November 2014 and a response was received from the applicant on 23 January 2014.

Microbiology Comment:
We refer to your 24 September 2014 submission and the response to Question 1b. We note your request for an exemption from testing an additional 2 lots of drug product for antimicrobial effectiveness based on the test results from [redacted] (b) (4)

filename: N207174R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability - Recommended for 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 (b) (4) The 2 mL presentation is labeled for multi dose use but both 1 mL presentations are single use. There is no difference in the formulation between the 1 mL and 2 mL presentations.

B. Brief Description of Microbiology Deficiencies – Not applicable.

C. 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[3]	Severity of Effect (S)	Detect. (D)	Risk Priority Number[6] (RPN)	Additional Review Emphasis based on Risk (in addition to normal review process)
Ster.	(b) (4)	6	-1	5	5	125	CCI (b) (4)
Endo		4		4	4	64	

3 = Anti-Microbial Formulation (e.g., meets USP <51>), modifies O (-1) [less emphasis on in process hold times]

6 = RPN = O(after modification when applicable)×S×D

RPN <50 = Low Risk; RPN 50-120 = Moderate Risk; RPN >120 = High Risk

B. Final Risk Assessment – This manufacturing process has been validated to support a sterile (b) (4) drug product. The (b) (4) The multi dose presentation is supported by adequate preservative effectiveness studies.

IV. Administrative

A. Reviewer's Signature _____
Jessica Cole, PhD

B. Endorsement Block _____
Bryan Riley, PhD
Microbiology Team Leader

C. CC Block
N/A

Product Quality Microbiology Assessment

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

S DRUG SUBSTANCE

The non-sterile powdered drug substance has a microbial limits specification.

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- **Description of drug product** – Sterile, preserved solution for injection in a 2 mL glass vial.
- **Drug product composition** –

Table 1- Drug product composition (Sponsor Table 2 Module 3.2.P.1)

Ingredients	2 mcg/mL	5 mcg/mL		Function	Reference to quality standards
	Quantity per 1 mL	Quantity per 1 mL	Quantity per 2 mL		
Paricalcitol	2.0 mcg[1]	5.0 mcg[1]	10.0 mcg[1]	Active	USP
Propylene Glycol	0.30 mL[2]	0.30 mL[2]	0.60 mL[2]	(b) (4)	USP & Ph.Eur#
Alcohol (Ethanol)	0.35 mL[3]	0.35 mL[3]	0.70 mL[3]	(b) (4)	USNF & Ph.Eur#
(b) (4)					

Packaging material description of Paricalcitol Injection, 2 mcg/mL (1 mL) and 5 mcg/mL (1 mL and 2 mL)	
Container description	2 mL, clear glass vial (type I)
Closure description	(b) (4) rubber stopper (b) (4)

USP: United States Pharmacopoeia
USNF: United States National Formulary
Ph. Eur: European Pharmacopoeia

(b) (4)

We are committing reference quality standards for the excipients USP/USNF grade only.

- **Description of container closure system** – See Table 1 above. The vial is supplied by (b) (4) and the stopper is supplied by (b) (4).

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/s/

JESSICA COLE
01/26/2015

BRYAN S RILEY
01/26/2015
I concur.

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 207-174 **Applicant:** Accord Healthcare Inc. **Letter Date:** 01 April 2014

Drug Name: Paricalcitol Injection **NDA Type:** 505(b)(2) **Stamp Date:** 01 April 2014

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		
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	X		(b) (4)
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		This is a multi dose vial preserved with 35% ethanol.
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		
7	Has the applicant submitted the results of analytical method verification studies?	X		Method verification studies are in Module 3.2.R.3.P.
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?			Not applicable.
9	If sterile, are extended post-constitution and/or post-dilution hold times in the draft labeling supported by microbiological data?			Not applicable. This product is preserved.
10	Is this NDA fileable? If not, then describe why.	X		

Additional Comments: This NDA describes two strengths (2 μg/mL and 5 μg/mL) of Paricalcitol. The 2 μg/mL formulation will be available in a 1 mL configuration and the 5 μg/mL formulation will be available in a 1 mL and 2 mL configuration. All 3 presentations use the same 2 mL glass vial with rubber stopper. The applicant is labeling the 2 mL presentation as a multidose vial while the 1 mL presentations are labeled as single dose vials.

Jessica G. Cole, PhD	22 April 2014
Reviewing Microbiologist	Date
Bryan Riley, PhD	
Microbiology Team Leader	Date

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

/s/

JESSICA COLE
04/23/2014

BRYAN S RILEY
04/23/2014
I concur.