CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206628Orig1s000

MICROBIOLOGY/VIROLOGY REVIEW(S)

Product Quality Microbiology Review

27 APR 2015

NDA: 206-628

Drug Product Name
Non-proprietary: Dexmedetomidine Hydrochloride Injection

Review Number: 2

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
21 APR 2015	21 APR 2015	23 APR 2015	23 APR 2015

Submission History (for 2nd Reviews or higher)

Submit Date(s)	Microbiology Review #	Review Date(s)
12 MAY 2014	1	09 MAR 2015
01 JUL 2014	1	09 MAR 2015
29 SEP 2014	1	09 MAR 2015
15 DEC 2014	1	09 MAR 2015
08 JAN 2015	1	09 MAR 2015
02 MAR 2015	1	09 MAR 2015

Applicant/Sponsor

Name: HQ Specialty Pharma Corporation
Address: 120 Route 17 North
Paramus, NJ 07652
Representative: Joseph Pizza
Telephone: 201-857-8290
Fax: 201-857-8291

Name of Reviewer: Jessica G. Cole, PhD

Conclusion: Recommended for Approval

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Class 2 resubmission

2. SUBMISSION PROVIDES FOR: Response to the 12 March 2015 complete response letter issued by the Agency

3. MANUFACTURING SITE:

(b) (4)

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

- 4 mL and 10 mL 0.1 mg/mL solution in a 5 mL or 10 mL glass vial
- Intravenous infusion
- Multi-dose preserved sterile solution

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

6. PHARMACOLOGICAL CATEGORY: Surgical sedative for non-intubated patients

B. SUPPORTING/RELATED DOCUMENTS: Microbiology review #1 of NDA 206-628 dated 09 March 2015

C. REMARKS: This submission was in the eCTD format

filename: N206628R2.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 – This is a sterile solution manufactured (b) (4). Both presentations are multi-dose vials.

B. Brief Description of Microbiology Deficiencies – Not applicable.

C. Assessment of Risk Due to Microbiology Deficiencies – Not applicable.

D. Contains Potential Precedent Decision(s)- ☐ **Yes** ☒ **No**

III. Administrative

A. Reviewer's Signature _____
Jessica G. Cole, PhD

B. Endorsement Block _____
Dupeh Palmer, PhD
Microbiology Secondary Reviewer

C. CC Block
In DARRTS

Product Quality Microbiology Assessment

The complete response letter for the first review cycle of NDA 206-628 contained the following deficiency (in italics). The class 2 resubmission response is summarized below the deficiency.

This application does not provide data that demonstrate the preservative system for the multi-dose vials is effective at the minimum proposed preservative content. The data submitted in the March 6, 2015, amendment did not include USP<51> data on Escherichia coli. *The justification you have provided that "*E. coli *is appropriate when testing oral preparations but not injections" is unacceptable as the USP<51> compendial test does not allow for alterations to the panel of test organisms. As requested in the December 19, 2014, information request, the proposed minimum preservative content should be supported by complete test results from USP<51> Antimicrobial Effectiveness Testing.*

The applicant has submitted USP<51> test results using the same method and formulation as that described and found acceptable in the 03 March 2015 amendment under review cycle #1. The test was conducted with a batch containing (b) (4) methyl parahydroxybenzoate and (b) (4) propyl parahydroxybenzoate. The data for *E. coli,* and the same data presented in the 03 March 2015 amendment, are shown in Table 1.

Table 1- Antimicrobial Effectiveness Test Data (Sponsor table from section 6 of the reviewers guide)

Test microorganism	Number of test micro-organisms in the inoculum cfu/ml	Log reduction				Comply with USP
		0 d	7 d	14 d	28 d	
Staphylococcus aureus	(b) (4)		NR	NR	NR	Yes
Pseudomonas aeruginosa			NR	NR	NR	Yes
Escherichia coli			NR	NR	NR	Yes
Candida albicans			NR	NR	NR	Yes
Aspergillus brasiliensis			NR	NR	NR	Yes

NR: No Recovery in number of viable test microorganisms.

ADEQUATE

REVIEWER COMMENT – The results demonstrate that the product meets the USP<51> requirements at the minimum preservative levels in the specification.

LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

None.

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/s/

JESSICA COLE
04/29/2015

DUPEH G Palmer-Ochieng
04/29/2015

Product Quality Microbiology Review

09 MAR 2015

NDA: 206-628

Drug Product Name
Non-proprietary: Dexmedetomidine Hydrochloride Injection

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
12 MAY 2014	12 MAY 2014	13 MAY 2014	16 MAY 2014
01 JUL 2014	01 JUL 2014	N/A	N/A
29 SEP 2014	29 SEPT 2014	N/A	N/A
15 DEC 2014	15 DEC 2014	N/A	N/A
08 JAN 2015	08 JAN 2015	N/A	N/A
02 MAR 2015	02 MAR 2015	N/A	N/A

Applicant/Sponsor
Name: HQ Specialty Pharma Corporation
Address: 120 Route 17 North
Paramus, NJ 07652
Representative: Joseph Pizza
Telephone: 201-857-8290

Name of Reviewer: Jessica G. Cole, PhD

Conclusion: Recommended as Approvable Pending a Complete Response to Microbiology Deficiencies

Product Quality Microbiology Data Sheet

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

2. SUBMISSION PROVIDES FOR: New drug product

3. MANUFACTURING SITE:

(b) (4)

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

- 4 mL and 10 mL 0.1 mg/mL solution in a 5 mL or 10 mL glass vial
- Intravenous infusion
- Multi-dose preserved sterile solution

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

6. PHARMACOLOGICAL CATEGORY: Surgical sedative for non-intubated patients

B. SUPPORTING/RELATED DOCUMENTS: None

C. REMARKS: This submission is in the eCTD format. The following information request was sent to the project manager on 28 August 2014 and a response was received on 29 September 2014.

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

1. We refer to the microbial ingress test conducted on the proposed container closure system. Provide the following information:
   a. A description of the positive control vials
   b. The incubation conditions (time and temperature) for the growth promotion units
2. We note that the manufacturing process does not include evaluation of the bioburden in the bulk solution (b) (4) Justify the lack of a (b) (4) bioburden sample.
3. Provide the maximum hold time(s) for the bulk solution prior to (b) (4) process.
4. Provide a description of the environmental monitoring program. Include the media and incubation conditions as well as the proposed levels for viable and non-viable monitoring.
5. Provide the method verification studies for the sterility and endotoxin release tests.
6. Provide a more detailed summary of the test procedure and the results from the USP<51> antimicrobial effectiveness tests.

The following information request was sent to the project manager on 17 November 2014 and a response was received on 15 December 2015.

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

1. We refer to Module 3.2.P.2.2 Table 5. Antimicrobial effectiveness data should support the minimum preservative content in the specification. The product specification requires (b) (4) % of each preservative, which corresponds to a minimum of (b) (4) methyl parahydroxybenzoate and (b) (4) propyl parahydroxybenzoate. The data provided in Table 5 do not support the proposed minimum specification for preservative content. Provide data that demonstrates that product with the minimum preservative content, or below, meets the USP<51> requirements.
2. We refer to the proposed package insert. Provide a maximum hold time for the diluted product prior to the start of the infusion. We recommend that this product be used immediately after dilution. Hold times in excess of 4 hours at room temperature or 24 hours under refrigeration should be supported with microbiological challenge data.

The following information request was sent to the project manager on 19 December 2014 and a response was received on 08 January 2015 and 03 March 2015.

> We refer to your 15 December 2014 amendment and the response to question 1 from the 17 November 2014 microbiology information request. We note your inclusion of antimicrobial effectiveness data from a similar drug product, (b) (4) that contained (b) (4) methyl parahydroxybenzoate and (b) (4) propyl parahydroxybenzoate. While these data were adequate for the (b) (4) product, the applicability to your proposed product, 0.1 mg/mL dexmedetomidine hydrochloride, is not clear. If the dexmedetomidine hydrochloride contributes to the overall antimicrobial effectiveness of the final drug product, then the data generated with the (b) (4) product may not be applicable to the 0.1 mg/mL product. Either provide data that demonstrates no antimicrobial effects are contributed by the dexmedetomidine hydrochloride or provide data that demonstrates that 0.1 mg/mL dexmedetomidine hydrochloride with the minimum preservative content, or below, meets the USP<51>requirements.

filename: N206628R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability - Recommended as Approvable Pending a Complete Response to Microbiology Deficiencies.

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 – This is a sterile solution manufactured [redacted] (b) (4). Both presentations are multi-dose vials.

B. Brief Description of Microbiology Deficiencies – The preservative effectiveness studies have not been conducted to support the multi-dose labeling.

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 (RPN)	Additional Review Emphasis based on Risk (in addition to normal review process)
Ster.	[redacted] (b) (4)					125	CCI at max cycle; flexible container port sterilization; less emphasis on in-process hold times
Endo						64	

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

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

B. Final Risk Assessment – This multi-dose product has not been demonstrated to be adequately preserved and as such, the potential risk to patients is unacceptable.

IV. Administrative

A. Reviewer's Signature Jessica G. Cole, PhD

B. Endorsement Block Stephen Langille, PhD
Microbiology Acting Branch Chief

C. CC Block In DARRTS and Panorama

Product Quality Microbiology Assessment

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

S DRUG SUBSTANCE

The synthetic non-sterile drug substance has a microbial and endotoxin specification.

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- **Description of drug product** – Sterile preserved solution in a 10 mL or 5 mL vial. The 10 mL vial is filled with 10 mL and the 5 mL vial is filled with 4 mL.
- **Drug product composition** –

Table 1- Composition of the drug product

Ingredient	mg/mL	mg per 4 mL vial	mg per 10 mL vial
Dexmedetomidine (base) weighed as:	0.100 mg (base)	0.4	1.0
Dexmedetomidine hydrochloride	0.118 mg	0.472	1.18
Methylparaben	1.6	6.4	16.0
Propylparaben	0.2	0.8	2.0
Sodium chloride	9.0	36.0	90
WFI	q.s. 1 mL	q.s. 4 mL (target fill is (b) (4))	q.s. 10 mL (target fill is (b) (4))

- **Description of container closure system** – The 5 mL and 10 mL type I tubular clear glass vials are closed with a (b) (4) coated (b) (4) rubber stopper with an aluminum seal.

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/s/

JESSICA COLE
03/09/2015

STEPHEN E LANGILLE
03/09/2015

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 206-628 **Applicant:** HQ Specialty Pharma Corporation **Letter Date:** 12 May 2014

Drug Name: Dexmedetomidine hydrochloride injection **NDA Type:** 505(b)(2) **Stamp Date:** 12 May 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		(b) (4) [redacted]
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	X		
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		Preserved multidose product
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 were not submitted
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 for this preserved multi dose product
10	Is this NDA fileable? If not, then describe why.	X		

Additional Comments: The drug product is a 4 mL fill in a 5 mL vial or a 10 mL fill in a 10 mL vial.

Information request for the sponsor:
1. Provide the method verification studies for the sterility and endotoxin release tests.
2. Provide the results from the USP<51> antimicrobial effectiveness tests.

Jessica Cole	09 June 2014
Reviewing Microbiologist	Date
Microbiology Secondary Reviewer/Team Leader	Date

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/s/

JESSICA COLE
06/09/2014

BRYAN S RILEY
06/09/2014
I concur.