CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203794Orig1s000

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

7 AUGUST 2012

NDA: 203794/N-000

Drug Product Name
Proprietary: NUCYNTA
Non-proprietary: Tapentadol Hydrochloride

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
15 December 2011	15 December 2011	6 January 2012	13 January 2012
7 May 2012	7 May 2012	N/A	N/A
13 June 2012	13 June 2012	N/A	N/A

Submission History (for amendments only): N/A

Applicant/Sponsor
Name: Janssen Pharmaceuticals, Inc.
Address: 1125 Trenton-Harbourton Road, P.O. Box 200
Titusville, NJ 08560-0200
Representative: Peggy Ferrone
Telephone: 908-704-5116

Name of Reviewer: Bryan S. Riley, Ph.D.

Conclusion: Recommend Approval

Product Quality Microbiology Data Sheet

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

2. SUBMISSION PROVIDES FOR: A new oral solution drug product

3. MANUFACTURING SITE: (b) (4)

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Non-sterile, aqueous solution for oral administration in a HDPE bottle, 100mL in a 120 mL bottle or 200 mL in a 235 mL bottle, 20 mg/mL.

5. METHOD(S) OF STERILIZATION: N/A

6. PHARMACOLOGICAL CATEGORY: Analgesic

B. SUPPORTING/RELATED DOCUMENTS: N/A

C. REMARKS: This was an eCTD submission. Information requests were sent to the applicant via email on 20 April 2012 and 6 June 2012. The text of the Product Quality Microbiology questions is provided below:

20 April 2012 IR

1. The drug product microbiological specifications should clearly identify the acceptance criteria both for enumeration and specific microorganisms. Merely stating that the drug product meets Current USP <1111> is not sufficient.

2. Provide test methods and acceptance criteria to demonstrate the product is free of the objectionable microorganisms of the *Burkholderia cepacia* complex. We recommend that potential sources are examined and sampled as process controls, and these may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria. Your test method should be validated and a discussion of those methods should be provided. Test methods validation should address multiple strains of the species and cells that are acclimated to the environments (e.g., warm or cold water) that may be tested.

3. Your proposal to perform skip lot testing for the Microbial Limits test is unacceptable because it does not comply with 21 CFR 211.165(a) and (b). Microbial limits testing should be performed on each lot of drug product at release. After obtaining sufficient data to demonstrate control of drug product bioburden, you may submit a prior approval supplement proposing to omit finished product microbial limits testing for batch release.

Reference ID: 3170974

After approval of omitting microbial limits testing at release, microbial limits testing should continue to be performed at the initial time point (at a minimum) on stability samples.

6 June 2012 IR
Your proposal to perform skip lot testing for the Microbial Limits test is unacceptable because it does not comply with 21 CFR 211.165(a) and (b). An attribute listed in the drug product specifications must be assessed for each lot of drug product at release by performing the appropriate test procedure. Therefore, the proposal to use skip lot testing for microbial limits should be withdrawn from your application.

However, after obtaining sufficient manufacturing experience and acceptable microbial limits testing data to demonstrate control of drug product bioburden, you may submit a prior approval supplement proposing to omit finished product microbial limits testing for batch release. After approval of omitting microbial limits testing from the release specification, microbial limits testing should continue to be performed at the initial time point (at a minimum) on stability samples.

> The applicant responded with amendments dated 7 May 2012 and 13 June 2012. The review of the amendments is included in section 3.2.P.5.

filename: N203794R1.doc

Reference ID: 3170974

Executive Summary

I. Recommendations

A. Recommendation on Approvability – This submission is recommended for approval on the basis of product quality microbiology.

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 a non-sterile oral liquid. Although the drug product does not contain a specific preservative, it meets the acceptance criteria for USP Chapter <51>. The drug product is tested for microbial limits at release.

B. Brief Description of Microbiology Deficiencies – N/A

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

III. Administrative

A. Reviewer's Signature _____

Bryan S. Riley, Ph.D.
Senior Review Microbiologist, OPS/NDMS

B. Endorsement Block _____

Stephen E. Langille, Ph.D.
Senior Review Microbiologist, OPS/NDMS

C. CC Block

N/A

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/s/

BRYAN S RILEY
08/07/2012

STEPHEN E LANGILLE
08/08/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 5 June 2012

TO: Luz Rivera, Project Manager, (ONDQA)

FROM: Bryan S. Riley, Ph.D., Senior Review Microbiologist (OPS/NDMS)

THROUGH: Stephen E. Langille, Ph.D., Senior Review Microbiologist (OPS/NDMS)

CC: DARRTS

SUBJECT: NDA 203794 - Product Quality Microbiology Information Request

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An information request addressing 3 product quality microbiology issues was sent to the applicant via email on 20 April 2012. The applicant responded by submitting an amendment to the NDA on 7 May 2012. Two of the three product quality microbiology issues were adequately addressed in the amendment.

The third product quality microbiology issue in the 20 April IR was related to the use of skip-lot testing for microbial limits. The applicant was informed that skip-lot testing was not acceptable because it did not conform with 21 CFR 211.165(a) and (b). However, the applicant responded by restating the justification for skip-lot testing contained in their original submission. Therefore, the following information request should be sent to the applicant:

> **Your proposal to perform skip lot testing for the Microbial Limits test is unacceptable because it does not comply with 21 CFR 211.165(a) and (b). An attribute listed in the drug product specifications must be assessed for each lot of drug product at release by performing the appropriate test procedure. Therefore, the proposal to use skip lot testing for microbial limits should be withdrawn from your application.**
>
> **However, after obtaining sufficient manufacturing experience and acceptable microbial limits testing data to demonstrate control of drug product bioburden, you may submit a prior approval supplement proposing to omit finished product microbial limits testing for batch release. After approval of omitting microbial limits testing from the release specification, microbial limits testing should continue to be performed at the initial time point (at a minimum) on stability samples.**

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/s/

BRYAN S RILEY
06/05/2012

STEPHEN E LANGILLE
06/06/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 18 April 2012

TO: Khushboo Sharma, Project Manager, (ONDQA)

FROM: Bryan S. Riley, Ph.D., Senior Review Microbiologist (OPS/NDMS)

THROUGH: Stephen E. Langille, Ph.D., Senior Review Microbiologist (OPS/NDMS)

CC: DARRTS

SUBJECT: NDA 203794 - Product Quality Microbiology Information Request

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The specifications for the drug product include the following section:

Table 1: Specifications for Tapentadol Oral Solution, 20-mg/mL

Test Parameter	Acceptance Criteria	Test Method
7. Microbiological Purity[b]		
a. Microbial enumeration tests	Current USP <1111>	Current USP <61>
b. Specific microorganisms	Current USP <1111>	Current USP <62>

[a] Tested at release only
[b] Test Frequency: monitoring frequency (minimum one batch per year) based on a microbiological risk assessment. See Justification of Specifications

The submission also states (section 3.2.P.5.6 Justification of Specifications) that the applicant will test, at a minimum, the first 10 production batches of the drug product for microbiological purity and use the results to generate data for a risk assessment. Skip lot testing would not be implemented until the risk has been determined to be low.

Reviewer Comment: **The drug product microbiological specifications should clearly identify the acceptance criteria both for enumeration and specific microorganisms. Merely stating that they meet Current USP <1111> is not sufficient. The drug product microbiological specifications should also include a test for the**

Reference ID: 3118936

opportunistic pathogens in the *Burkholderia cepacia* complex. Additionally, skip lot testing is unacceptable because it does not comply with 21 CFR 211.165(a) and (b).

Comments to be sent to the Applicant:

1. The drug product microbiological specifications should clearly identify the acceptance criteria both for enumeration and specific microorganisms. Merely stating that the drug product meets Current USP <1111> is not sufficient.

2. Provide test methods and acceptance criteria to demonstrate the product is free of the objectionable microorganisms of the *Burkholderia cepacia* complex. We recommend that potential sources are examined and sampled as process controls, and these may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria. Your test method should be validated and a discussion of those methods should be provided. Test methods validation should address multiple strains of the species and cells that are acclimated to the environments (e.g., warm or cold water) that may be tested

3. Your proposal to perform skip lot testing for the Microbial Limits test is unacceptable because it does not comply with 21 CFR 211.165(a) and (b). Microbial limits testing should be performed on each lot of drug product at release. After obtaining sufficient data to demonstrate control of drug product bioburden, you may submit a prior approval supplement proposing to omit finished product microbial limits testing for batch release. After approval of omitting microbial limits testing at release, microbial limits testing should continue to be performed at the initial time point (at a minimum) on stability samples.

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/s/

BRYAN S RILEY
04/19/2012

STEPHEN E LANGILLE
04/19/2012

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 203794 **Applicant:** Janssen Pharmaceuticals, Inc. **Letter Date:** 15 December 2011

Drug Name: NUCYNTA **NDA Type:** 505(b)(1) **Stamp Date:** 15 December 2011

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		
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		AME testing was provided in section P.2.5
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	
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?	X		
9	Is this NDA fileable? If not, then describe why.	X		

Additional Comments: The drug product is a non-sterile, aqueous, oral solution. The applicant is proposing skip-lot testing for microbial limits and is not testing for *Burkholderia cepacia*. An IR will be drafted to send to the applicant regarding skip-lot testing and *B. cepacia*.

26 January 2012

Bryan S. Riley, Ph.D.
Senior Review Microbiologist — Date

John W. Metcalfe
Senior Review Microbiologist — Date

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/s/

BRYAN S RILEY
01/28/2012

JOHN W METCALFE
01/30/2012
I concur.