CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022396Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

Product Quality Microbiology Review

02 August 2010

NDA: 22-396/N-000

Drug Product Name
Proprietary: Dyloject™
Non-proprietary: Diclofenac sodium injection.

Review Number: 1.

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
02 DEC 2009	03 DEC 2009	23 DEC 2009	30 DEC 2009
08 APR 2010	08 APR 2010	N/A	N/A

Applicant/Sponsor
Name: Javelin Pharmaceutical, Inc.
Address: 125 Cambridge Park Dr.
Cambridge, MA. 02140
Representative: Roberta Tucker
Telephone: 508-842-9339

Name of Reviewer: John W. Metcalfe, Ph.D.

Conclusion: Recommend approval.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: An original NDA.

2. SUBMISSION PROVIDES FOR: A new drug product.

3. MANUFACTURING SITE:
(b) (4)

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

- 1 mL sterile solution in 2 mL glass vial.
- Intravenous (b) (4) injection.
- 37.5 mg/mL.

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

6. PHARMACOLOGICAL CATEGORY: The subject drug product is indicated for the management of acute moderate to severe pain.

B. SUPPORTING/RELATED DOCUMENTS: Microbiology Reviews of DMF (b) (4) (dated 08 August 2007 & 12 December 2008).

C. REMARKS:
The NDA is submitted electronically in the CTD format.

A Microbiology Information Request was forwarded to the applicant by the OND Project Manager on 10 March 2010. Following is the Information Request:

> A microbiology review of NDA 22-396/N-000 is in progress. Please provide the following information or reference to its location in the subject submission:
>
> - The test method and acceptance criterion (b) (4)
> - The duration of the holding periods (b) (4) Include data or a rationale in support of these holding periods.

The applicant amended the NDA with responses to this request on 08 April 2010. The responses are summarized and reviewed in appropriate sections of this review.

File Name: N022396R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – NDA 22-396/N-000 is recommended for approval on the basis of product quality microbiology.

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 - (b) (4)

B. Brief Description of Microbiology Deficiencies – There are no microbiology deficiencies identified.

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

III. Administrative

A. Reviewer's Signature _____
John W. Metcalfe, Ph.D.

B. Endorsement Block_____
Bryan S. Riley, Ph.D.

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 drug substance manufacturing process is [redacted] (b) (4)

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- **Description of drug product**
  The subject drug product is a sterile solution in glass vial.

- **Drug product composition**
  The composition of the subject drug product is presented in Table 1.

Table 1. Drug Product Composition.

Ingredient	Amount (mg/1 mL)	Concentration (% w/v)	Function	Reference
Diclofenac Sodium	37.5	3.75	Drug substance	USP
Hydroxypropyl-Betadex	333			NF
Monothioglycerol	5.0	0.5		NF
Hydrochloric Acid/ Sodium Hydroxide			pH adjustment	NF
Water for Injection				USP

(b) (4)

Reviewer's Comment

[redacted] (b) (4)

- **Description of container closure system**
  The drug product container closure system consists of the following:
  - Container: 2 mL Type I glass vial [redacted] (b) (4)
  - Closure: 13 mm [redacted] (b) (4) rubber stopper [redacted] (b) (4)
  - Seal: 13 mm aluminum overseal [redacted] (b) (4)

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- **Container-Closure and Package integrity**

(b) (4)

(b) (4). Data from this container closure integrity study are provided in the Report and are acceptable.

Satisfactory

(b) (4)

P.3 Manufacture

P.3.1 Manufacturers

(b) (4)

P.3.3 Description of the Manufacturing Process and Process Controls

(b) (4)

(b) (4)

- **Sterilization/Depyrogenation of containers, closures, equipment and components**

(b) (4)

- **Environmental monitoring**

(b) (4) [redacted] (b) (4) Environmental monitoring is performed at the manufacturing site according to internal SOPs. (b) (4) [redacted] (b) (4) [redacted] (b) (4). Finally, environmental monitoring data from three process simulations and the manufacture of 4 submission lots (P117038Z, P018055Z, P018059Z and P028060Z) are linked to the narrative. The data are acceptable.

Satisfactory

P.3.5 Process Validation and/or Evaluation

(b) (4) [redacted]

(b) (4)

[redacted]

The data from the three test runs which comprised this validation are presented in tables within the validation report and are acceptable.

Satisfactory

- **Sterilization/Depyrogenation of containers, closures, equipment and components**

(b) (4)

[redacted]

(b) (4)

Data from the container depyrogenation/sterilization process are presented in tables in the General Technical Report and are acceptable.

Satisfactory

(b) (4)

➢

documented.

Data from this validation are presented in tables within General Technical Report 49578 and meet stated acceptance criteria.

Satisfactory

(b) (4)

Data from this validation are presented in tables within General Technical Report 49323 and meet stated acceptance criteria with the exception of one deviation.

Satisfactory

Reviewer's Comment

The deviation is summarized as follows by the applicant. (b) (4)

(b) (4) In this reviewer's opinion, this one study deviation is not an indicator that (b) (4) is inadequate.

- **Holding periods**
  The bulk solution holding time (b) (4) is (b) (4) hours (Module 3.2.P.2.3.3). In support of this holding time, the applicant performed bioburden testing on 4 batches of product (#s 117038, 018055, 018059 and P028060) at the (b) (4) hour time point (Table 3.2.P.2.3-15). Each of the 4 batches of product had a bioburden level (b) (4)

Satisfactory

Reviewer's Comment
The total manufacturing holding time (b) (4) (b) (4) does not present a risk to the microbiological quality of the subject drug product.

- **Media fill procedures and specification**
  (b) (4) (b) (4) The applicant follows internal SOP (b) (4) when performing media fills. (b) (4) (b) (4)

Data from three media fill process simulations performed in the summer of 2008 in support of the subject drug product manufacturing process are presented in Table 11 of the narrative and are acceptable.

Satisfactory

- **Actions concerning product when media fills fail**
  The applicant states that a failed media fill will stimulate an investigation which includes the following:
  [redacted] (b) (4)

  The investigation is conducted by the Quality and Production departments.

P.5 Control of Drug Product

P.5.1 Specification

The product specification includes the test methods and acceptance criteria shown in Table 2 which are indicators of the microbiological quality of the subject drug product.

Table 2. Microbiological Tests and Acceptance Criteria.

Test	Method	Release Acceptance Criteria	Stability Acceptance Criteria
Sterility	USP<71>	Sterile	Sterile
Bacterial Endotoxins	USP<85>, Gel Clot	NMT [redacted] (b) (4) EU/mL (IU/mL)	NMT [redacted] (b) (4) EU/mL (IU/mL)
Container-Closure Integrity*	Visual	No Leakage	No Leakage

* [redacted] (b) (4)

P.5.2 Analytical Procedures

- **Endotoxin**
  The applicant tests the drug product for the presence of endotoxins using the gel clot method according to USP<85> and has established a bacterial endotoxin acceptance criterion of NMT [redacted] (b) (4) EU/mL. The recommended dose for the subject drug product is 37.5 mg administered by IV or bolus injection. Treatment may be repeated every 6 hours (Module 1.14). Since the concentration of the subject drug product is 37.5 mg/mL, a dose of 37.5 mg converts to an injection of 1 mL of the drug product. Incorporation of this dose into the equation referenced in USP <85> for endotoxin limit determination (Endotoxin Limit = K/M, where K is the threshold human pyrogenic dose per kg body weight per hour and M is the maximum recommended human product dose per kg of body weight per hour for a 70 kg human) results in an endotoxin limit of [redacted] (b) (4) EU/mL drug.

$$\text{Endotoxin limit} = \frac{\text{[redacted] (b) (4)}}{1\ \text{mL}/70\ \text{kg BW/Hr}} = \text{[redacted] (b) (4) EU/mL.}$$

The applicant's established limit of (b) (4) EU/mL therefore provides a margin of safety regarding bacterial endotoxin pyrogenicity.
A verification study of the suitability of use of the stated gel clot assay with the subject drug product was performed by the LAL provider (b) (4) An internal SOP (b) (4) was followed for this purpose. (b) (4)

Three product lots (C077072, 117038 and 018055) were tested in the validation. (b) (4)

Data from this verification are provided in tables in the Validation Report. The data are acceptable in demonstrating that the product neither enhances nor inhibits the gel clot method.

Satisfactory

- **Sterility**
  The finished drug product is tested for sterility according to USP<71> (b) (4)

The suitability of use of the stated sterility method with the subject drug product was verified according to USP<71>. Three lots (C077072, 117038 and 018055) were used for the verification studies. The following challenge microbes were used in the verification:

- *Aspergillus niger.*
- *Candida albicans.*
- *Bacillus subtilis.*
- *Pseudomonas aeruginosa.*
- *Clostridium sporogenes.*
- *Staphylococcus aureus.*
- *Staphylococcus epidermidis.*

Data from this verification are provided in tables in Exhibit 12 of the Sterilization Validation Report and are acceptable.

Satisfactory

P.7 Container Closure System

Reference is made to Section P.1 of this review.

P.8 Stability

P.8.1 Stability Summary and Conclusion

Seven batches of product (#117038, 117038Z, 018055, 018059, 018059Z, P028060 and P028060Z) were manufactured at the proposed manufacturing site and placed into the stability testing program. The batches are stored at (b) (4) RH and (b) (4) monitored (b) (4) RH. The testing of these stability samples which is a measure of the microbiological quality of the subject drug product includes the following:

- Sterility: release, 6, 12, 24 and 36 months.
- Bacterial endotoxins: release, 3, 6, 9, 12, 18, 24, 30 and 36 months.
- Container closure integrity: release, 3, 6, 9, 12, 18, 24, 30 and 36 months.

P.8.2 Post-Approval Stability Protocol and Stability Commitment

The applicant commits to completing the stability testing program which is described in Section P.8.1 of this review, and will submit future data to the NDA. (b) (4) The post approval stability testing protocol for commercial production of the subject drug product is presented in Table 3.

Table 3. Post Approval Stability Protocol (b) (4)

(b) (4)

P.8.3 Stability Data

The subject submission contains 12 months of data from the testing of the batches placed into the stability program. Data from the stability testing are presented in tables in Module 3.2.P.8.3 of the subject submission. To

date, the stability testing which is indicative of the drug product's microbiological quality meets stated acceptance criteria.

Satisfactory

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

Not applicable.

A.2.1 [redacted] (b) (4)

Not applicable.

A.2.2 Testing at Appropriate Stages of Production

Not applicable.

A.2.3 [redacted] (b) (4)

Not applicable.

A.2.4 Viral Clearance Studies

Not applicable.

R REGIONAL INFORMATION

R.1 Executed Batch Record

Copies of executed batch records are provided in Module 3.2.R of the subject submission.

2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

A. PACKAGE INSERT

The recommended dose stated in the draft label is 37.5 mg. Since the drug product is presented as a 1 mL fill with a concentration of 37.5 mg/mL, a dose of 37.5 mg is generated from one vial. [redacted] (b) (4)

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

There are no microbiology deficiencies identified.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22396	ORIG-1	HOSPIRA INC	diclofenac sodium injection

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/s/

JOHN W METCALFE
08/02/2010
Recommended for approval on the basis of Product Quality Microbiology.

BRYAN S RILEY
08/02/2010
I concur.

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 22-396/N-000 **Applicant:** Javelin Pharmaceuticals. **Letter Date:** 12/02/2009

Drug Name: diclofenac sodium injection. **NDA Type:** Possible Priority. **Stamp Date:** 12/03/2009

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 (CCI)		(b) (4)
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?			This reviewer is unaware of any requested pre-submission information.
9	Is this NDA fileable? If not, then describe why.	X		

Additional Comments: None.

John W. Metcalfe, Ph.D. Date

Stephen Langille, Ph.D. Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22396	ORIG-1	JAVELIN PHARMACEUTICALS INC	diclofenac sodium injection

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/s/

JOHN W METCALFE
01/25/2010

STEPHEN E LANGILLE
01/25/2010