CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202497Orig1s000

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

July 25, 2012

NDA: **202497**

Drug Product Name
Proprietary: Marqibo®
Proprietary: Vincristine Sulfate Liposomes Injection
Review Number: 2

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
May 3, 2012	May 3, 2012	April 30, 2012[@]	April 30, 2012

@ An advanced email copy was received by the Division and distributed to the Reviewers.

Submission History (for amendments only)

Submit Date(s)	Microbiology Review #	Review Date(s)
July 12, 2011	1	April 19, 2012

Applicant/Sponsor
Name: Talon Therapeutics
Address: 2207 Bridgepointe Parkway,
San Mateo, CA 94404
Representative: Thomas J Tarlow, Vice President, RA & QA
Telephone: 650-228-5066, fax 650-228-5067

Name of Reviewer: Vinayak B. Pawar, Ph.D.

Conclusion: Recommend approval.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original NDA

2. SUBMISSION PROVIDES FOR: An amendment to the New Drug Application.

3. MANUFACTURING SITE: Hospira Australia Pty Ltd, Mulgrave, Victoria 3170, Australia.
FDA (FEI): 3001174929.

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Vincristine Sulfate Liposomes Injection 0.16mg/mL is constituted from Marqibo® Kit which contains three components as described in Product Quality Microbiology Assessment Section P. Marqibo® is administered at a dose of 2.25 mg/m2 intravenously over 60 minutes every 7 days.

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

6. PHARMACOLOGICAL CATEGORY: Treatment of acute lymphoblastic leukemia.

B. SUPPORTING/RELATED DOCUMENTS: None

C. REMARKS: This amended submission by Talon Therapeutics is a response to four product quality microbiology deficiencies cited in the original review of NDA 202497. Deficiency #1 was sent to the sponsor in an IR letter on February 9, 2012 and again on March 28, 2012. Since the sponsor had not responded by April 19, 2012, this and three additional deficiencies were cited in the final review of NDA 202497 and conveyed to the sponsor in an IR dated April 25, 2012. The sponsor responded to all of the microbiology deficiencies in their submission dated May 3, 2012 and the responses are the subject of this review.

filename: **N202497R2**

Executive Summary

I. Recommendations

A. Recommendation on Approvability – Recommend 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 – (b) (4) The other two components SCLI and SPI which make up the Marquibo® kit are independently manufactured. These manufacturing processes were discussed in the original review. Only responses to the deficiencies are reviewed here.

B. Brief Description of Microbiology Deficiencies – None.

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

III. Administrative

A. Reviewer's Signature _____
Vinayak B. Pawar, Ph.D.

B. Endorsement Block _____
John W. Metcalfe, Ph.D.

C. CC Block
N/A

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/s/

VINAYAK B PAWAR
07/26/2012

JOHN W METCALFE
07/26/2012
I concur.

Product Quality Microbiology Review

April 11, 2012

NDA: **202497**

Drug Product Name
Proprietary: Marqibo®
Proprietary: Vincristine Sulfate Liposomes Injection
Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
July 12, 2011	July 12, 2011	August 2, 2011	August 4, 2011

Submission History (for amendments only) –N/A

Applicant/Sponsor
Name: Talon Therapeutics
Address: 2207 Bridgepointe Parkway,
San Mateo, CA 94404
Representative: Thomas J Tarlow, Vice President, RA & QA
Telephone: 650-228-5066, fax 650-228-5067

Name of Reviewer: Vinayak B. Pawar, Ph.D.

Conclusion: Approvable pending resolution of issues listed in Section 3 of this review.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original NDA

2. SUBMISSION PROVIDES FOR: A New Drug Application.

3. MANUFACTURING SITE: Hospira Australia Pty Ltd, Mulgrave, Victoria 3170, Australia.
FDA (FEI): 3001174929.

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Vincristine Sulfate Liposomes Injection 0.16mg/mL is constituted from Marqibo® Kit which contains three components as described in Product Quality Microbiology Assessment Section P. Marqibo® is administered at a dose of 2.25 mg/m2 intravenously over 60 minutes every 7 days.

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

6. PHARMACOLOGICAL CATEGORY: Treatment of acute lymphoblastic leukemia.

B. SUPPORTING/RELATED DOCUMENTS: None

C. REMARKS: Drug Product Marquibo® was submitted under NDA 21-600 by Tekmira Pharmaceuticals and received a non approval action in 2005. Talon addressed Quality and other issues from the Agency's enquiry and claims there are no outstanding issues from NDA 21-600 non approval letter that would prevent submission and acceptance for filing NDA 202497. The applicant is seeking accelerated registration of Marquibo® vincristine sulfate liposomes Injection through the electronic submission of this original NDA 202497. IQA was filed by CMC on 09/06/2011. On February 9, 2012 an IR was sent to the sponsor to request information on the aseptic handling of the Marquibo® kit during reconstitution in a pharmacy setting and to justify the post constitution storage of 12 hours through the absence of microbial growth. The justification for post constitution storage of 12 hours was provided on March 23, 2012. Information on aseptic handling of the Marquibo® kit during reconstitution in a pharmacy setting is pending to this date.

filename: **N202497R1**

Executive Summary

I. Recommendations

A. Recommendation on Approvability – Approvable pending resolution of issues listed in Section 3 of this review.

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 – [redacted] (b) (4) The other two components SCLI and SPI which make up the Marquibo® kit are independently manufactured and the manufacturing processes are discussed in the review.

B. Brief Description of Microbiology Deficiencies – The deficiencies pertain to the human factor involvement in the aseptic manipulations and preparation of the Marquibo kit and the lack of [redacted] (b) (4) process validation information from two components of this kit.

C. Assessment of Risk Due to Microbiology Deficiencies – Medium.

III. Administrative

A. Reviewer's Signature _____
Vinayak B. Pawar, Ph.D.

B. Endorsement Block _____
John W. Metcalfe, Ph.D.

C. CC Block
N/A

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/s/

VINAYAK B PAWAR
04/19/2012

JOHN W METCALFE
04/19/2012
I concur.

M E M O R A N D U M

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

DATE: **February 2, 2012**

TO: **Amy Baird, Regulatory Project Manager, OND/DHP/CDER**

FROM: **Vinayak B. Pawar, Ph.D., Senior Reviewer, New Drug Microbiology Staff, OPS**

THROUGH: **John W, Metcalfe, Ph.D., Senior Reviewer, New Drug Microbiology Staff, OPS**

SUBJECT: **Information Request at Mid-Cycle Review of NDA 202497**

In order to complete the product quality microbiology review of NDA 202497, the following issues need to be addressed with regard to the constitution of the drug product using the Marquibo® Kit.

1. For the constitution of the Marquibo kit, the contents of three separate sterile vials will be combined in the VSLI vial, heated at 65 + 2°C in a water bath for the eventual administration of the admixture with 5% Dextrose Injection or 0.9% Sodium Chloride Injection. What precautions will be taken to ensure that aseptic conditions will be maintained throughout the constitution process, in a pharmacy setting.

Comment: For the constitution of the Marquibo® Kit, three separate vials must be combined in a specific order, heated at a specified temperature of 65 + 2°C for specified time of 10 minutes. In addition, from microbiology product quality standpoint, the multiple manipulations will require materials such a water bath free of microbial contamination, sterile syringes and sterile venting filters. Although sterile syringes may be readily available in a pharmacy setting, sterile venting filters will need to be stocked and an established procedure should be in place to assure that the water bath remains free of microbial contamination.

2. The current label requires the constituted product to be used within 12 hours of constitution start time. Microbiological studies in support of the 12-hour post-constitution storage time (as stated in the proposed labeling) have not been provided. Please provide a risk assessment summarizing studies that show adventitious microbial contamination does not grow under the storage conditions. Reference is made to Guidance for Industry: ICH Q8 Pharmaceutical Development, Section II.E and Guidance for Industry: ICH Q1A(R2) Stability Testing of New Drug Substances and Products, Section 2.2.7.
http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html.

Generally, "no growth" is interpreted as not more than a 0.5 $\log_{10}$ increase from the initial count; however other evidence of growth may be significant. The test should be run at the label's recommended storage conditions, be conducted for 2 to 3-times the label's recommended storage period, and use the label-recommended fluids inoculated with low numbers (≤100 CFU/mL) of challenge microbes. Challenge organisms may include strains

described in USP <51> plus typical skin flora or species associated with hospital-borne infections. In lieu of these data, the product labeling should recommend that the post-constitution storage period is not more than 4 hours at room temperature.

Comment: When a product's container is penetrated, we acknowledge the risk of microbial contamination. We interpret this to mean that the applicant must demonstrate that the labeling recommends proper storage conditions for an admixture after the product was contaminated microbiologically, unless the dose will be used immediately. We use 4 hours as a base cut-off when defining "immediate use," based on the time required for common bacteria to enter into rapid growth phase.

A risk analysis should be done based on microbiological challenges to the product in recommended diluents. Also, if the vials are constituted and stored more than 4 hours, they too should undergo challenge studies. The applicant should determine what happens when microorganisms common to nosocomial infections are introduced into the product and then stored at various time and temperature conditions, and in all recommended diluents. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections. The applicant should also challenge product stored longer than recommended and at different temperatures (e.g., room temperature) to establish those risks.

END

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/s/

VINAYAK B PAWAR
02/02/2012

JOHN W METCALFE
02/03/2012
I concur.

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 202497 **Applicant:** Talon Therapeutics **Letter Date:** July 13, 2011

Drug Name: Marqibo Kit (vincristine sulfate liposome Injection) **NDA Type:** Original **Stamp Date:** July 13, 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		Manufacturing process is described in Section 3.2.P.3.3.5
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	X		Process validation studies are provided in Section 3.2.P.3.5
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		(b) (4) . Section 3.2.P.2.5 provides container-closure integrity studies.
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		Section 3.2.P.8.1, Table 2.
7	Has the applicant submitted the results of analytical method verification studies?	X		Section 3.2.P.5.3 provides validation of sterility & bacterial endotoxins methods.
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?			Not verifiable.
9	Is this NDA fileable? If not, then describe why.	X		

Additional Comments: The product is aseptically filled.

Reviewing Microbiologist: Vinayak B. Pawar, Ph.D. **Date**

Secondary Concurrence: Bryan S. Riley, Ph.D. **Date**

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/s/

VINAYAK B PAWAR
08/31/2011

BRYAN S RILEY
08/31/2011
I concur.