CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207793Orig1s000

MICROBIOLOGY/VIROLOGY REVIEW(S)

Product Quality Microbiology Review

29 September 2015

NDA: **207793/N000**

Drug Product Name
Proprietary: Onivyde
Non-proprietary: Irinotecan Liposome Injection

Review Number: #1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
3/31/2015	3/31/2015	N/A	4/4/2015
6/4/2015	6/4/2015	N/A	N/A
7/31/2015	7/31/2015	NA	NA

Submission History (for 2nd Reviews or higher)

Submit Date(s)	Microbiology Review #	Review Date(s)
n/a	n/a	n/a

Applicant/Sponsor
Name: Merrimack Pharmaceuticals, Inc.
Address: One Kendall Square, Suite B7201, Cambridge, MA 02139
Representative: Michael Slater
Telephone: Office: 617-441-7498; Cell: (b) (6)
Fax: 617-902-2540

Name of Reviewer: Haijing Hu, Ph.D.
Reassigned to Denise A. Miller

Conclusion: The submission is recommended for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUBMISSION:** Original

2. **SUBMISSION PROVIDES FOR:** Initial marketing of sterile drug product

3. **MANUFACTURING SITE:**

For [redacted] manufacturing and release testing
Merrimack Pharmaceuticals, Inc.
One Kendall Square Campus
1 Kendall Square Suite B7201
Cambridge, MA 02139-1670
Tel: 617.441.1000

For fill and finish
[redacted]

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Sterile injection, IV, 5mg/mL, packaged in 10 ml vials ([redacted]ml/vial), single-use vials (32P1, p2/3)

5. **METHOD(S) OF STERILIZATION:** [redacted]

6. **PHARMACOLOGICAL CATEGORY:** Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5- fluorouracil (5-FU) and leucovorin (LV), in patients previously treated with gemcitabine

B. **SUPPORTING/RELATED DOCUMENTS:**

Type III DMF [redacted]– for [redacted] review [redacted].doc by S. Steffen, Ph.D., dated 2/25/2013 (adequate)

Type V DMF [redacted]– for [redacted] fill facility [redacted], initial review by H. Hu, Ph.D., dated 6/10/2015 was not adequate pending a satisfactory response to an information request. The DMF holder's response to the IR was reviewed by D. Miller on 09/29/15 and was determined to be adequate.

Type III DMF # [redacted]– for container closure integrity test, reviewed by C. Thomas, Ph.D., dated 10/29/2009 (adequate)

C. **REMARKS:**

1) Dr. Hu was the primary reviewer of this application. The application was reassigned to Denise Miller for the review of the responses to the 07 July 2015 information request and for review finalization.

2) The application is electronic in CTD format. Some tables are copied from the submission into this review.

3) An information request (IR#1) was sent on 20 May 2015 for which a response was submitted on 04 June 2015. This was a multi-discipline IR in which the microbiology related question were items # 12 through 23.

4) A second IR (IR#2) was sent on 07 July 2015 for which a response was submitted on 31 July 2015.

Filename: 207793.doc
Template version: OGD modified_AP_2014v6.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability -

The submission is recommended for approval on the basis of sterility assurance.

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)

[redacted]

B. Brief Description of Microbiology Deficiencies – Please see the Deficiencies Section at the end of the review memo.

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, 4, 5]	Severity of Effect (S)	Detect. (D)	Risk Priority Number[6] (RPN)	Additional Review Emphasis based on Risk (in addition to normal review process)
(b) (4) [redacted]							

1 = A Closed Aseptic Process is one that has no exposed manipulations other than filling and stoppering after the components are sterilized. (e.g., RABS, isolator, closed drying and filling process for a powder)
2 = An Open Aseptic Process is one that has one or more steps with potential to contaminate the drug product after the component sterilizing. (e.g., sterile drug substance/excipient, interaction of operators

with sterile product path, traditional Class 100 filling area).
3 = Anti-Microbial Formulation (e.g., meets USP <51>), modifies O (-1) [less emphasis on in process hold times]
4 = Post-Constitution/-Dilution Hold Times in Labeling, modifies O (+1) [emphasize Labeling instructions for administration, dosing, storage conditions, and specified diluents. Microbial challenge studies supporting label recon/dilution/storage instructions if >4 hr RT or >24 hr refrig.]
5 = Components derived from animal sources, modifies O (+1) [emphasize Component bioburden, TSE/BSE-free documentation (TS and AP), viral inactivation studies (AP), bioburden reduction processes.]
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 - The applicant mitigated the sterility and endotoxin risks by adequately validating the (b) (4) process, establishing in-process controls, and establishing adequate microbiological tests and acceptance criteria for the drug product specifications.

IV. Administrative

A. Reviewer's Signature _____

B. Endorsement Block

Microbiologist/Haijing Hu, Ph.D.
Microbiologist/Denise A. Miller
Microbiology Secondary Reviewer/Neal J. Sweeney, Ph.D.

C. CC Block
cc: Field Copy

Product Quality Microbiology Assessment

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

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- **Description of drug product** – (32P1, p2/3)

  Sterile, white to slightly yellow opaque isotonic liposomal dispersion

- **Drug product composition** – (32P1, p3/3)

Component	Reference to Quality Standard	Function	Amount (mg/mL)
Irinotecan hydrochloride	USP	Active pharmaceutical ingredient	5.00
DSPC	In-house	Vesicle-forming lipid	6.81
Cholesterol	USP/Ph. Eur.	Vesicle-forming lipid	2.22
MPEG-2000-DSPE	In-house	Vesicle-forming lipid	0.12
2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulfonic acid (HEPES)	In-house	Buffer	4.05
Sodium chloride	USP/Ph. Eur.	Isotonicity agent	8.42
(b) (4)	USP/Ph. Eur.	(b) (4)	(b) (4)

DSPC stands for 1,2-Distearoyl-snglycero-3-phosphocholine

- **Description of container closure system** – (33P1 p3/3 and 32P7 p4/6)

Component	Description	Manufacturer
Vial	10 ml Type I, glass (Ph. Eur. and USP)	(b) (4)
Stopper	(b) (4)	
Seal	20 mm aluminum flip off seal with white plastic cap	

Acceptable

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- **Container-Closure and Package integrity (CCIT)** - (32R Media Fill Report p17/22)

17 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

Summary of Response: As noted in time 23, Merrimack agrees with the Agency and will limit the post constitution storage period to not more than 4 hours at room temperature or 24 hours at 2-8°C.

Reviewer Note: This has been the policy of the new drug microbiology group to allow this proposed dilution and storage time. A discussion between acting quality assessment lead John Arigo and acting branch chief Bryan Riley was held on 6/10/2015 and Bryan concurred that this is acceptable.

Acceptable

3. **MICROBIOLOGY COMMENTS:** The NDA is adequate in support of the aseptic manufacturing for the subject drug product.

Reviewer's Signature Denise Miller -A

Digitally signed by Denise Miller -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Denise Miller -A, 0.9.2342.19200300.100.1.1=2000286872
Date: 2015.09.29 10:47:32 -04'00'

Denise A. Miller
Microbiologist, OPQ/OPF/DMA/Branch II

Endorsement Block Neal J. Sweeney -A

Digitally signed by Neal J. Sweeney -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300109587, cn=Neal J. Sweeney -A
Date: 2015.09.29 10:50:57 -04'00'

Neal J. Sweeney
Sr. Microbiologist, OPQ/OPF/DMA/Branch II