

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207793Orig1s000

CHEMISTRY REVIEW(S)



CMC Memo to File

Date	16-Oct-15
Applicant	Merrimack Pharmaceuticals, Inc.
Drug:	Irinotecan liposome injection
NDA	207-793
Reviewer	Olen Stephens, Ph.D.

This close out memo captures Merrimack's follow-up on the information request sent 21-Sep-15. Amendment 0023 (submitted 9-Oct-15) contains changes to reflect the expression of strength on the basis of the irinotecan free base. The tables below capture the changes made to the CTD that convert calculations and data expression to the irinotecan free base. The changes does not change the overall recommendation from OPQ for approval of the NDA.

Changes to Section 1.11. 1 Information Amendment (Quality)

Section No. and Title	Currently on File	Proposed Change
Irinotecan Concentration	Calculated the irinotecan concentration based on the irinotecan HCl trihydrate	Updated to calculate the irinotecan concentration based on the irinotecan anhydrous free base
Percent Encapsulated Drug		
Drug to Phospholipid Ratio		
In Vitro Release		

Changes to Section 3.2.P.1 Description and Composition of the Drug Product

Section No. and Title	Currently on File	Proposed Change
Table 1	Irinotecan hydrochloride Trihydrate 5.00 mg/mL	Irinotecan (anhydrous free base) 4.33 mg/mL

Changes to Section 3.2.P.2.6 Compatibility

Section No. and Title	Currently on File	Proposed Change
3.2.P.2.6.2	(b) (4)	
3.2.P.2.6.3		

1 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

Section No. and Title	Currently on File	Proposed Change
(b) (4)		

Conclusion: The NDA is still recommended for approval from a CMC perspective. This amendment fulfills commitments to update CTD sections to reflect the strength representation based on the irinotecan free base.

Olen Stephens -S

Digitally signed by Olen Stephens -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Olen Stephens -S,
0.9.2342.19200300.100.1.1=2000558826
Date: 2015.10.19 08:33:50 -0400

Olen Stephens, Ph.D.
Chemistry Acting Branch Chief, ONDP



Recommendation: Approval

**NDA 207793
Onivyde (irinotecan liposome injection)
Review #1**

Drug Name/Dosage Form	Irinotecan/Onivyde Liposome Injection
Strength	4.3 mg/mL
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Merrimack Pharmaceuticals, Inc.

SUBMISSION(S) REVIEWED	DOCUMENT DATE
0000 Original Submission	April 24, 2015
0001 Quality Information	March 31, 2015
0002 Multiple Categories	April 24, 2015
0005 revised trade name	May 14, 2015
0006 Labeling	May 29, 2015
0007 CMC Response to IR	June 4, 2015
0008 Multiple Categories	June 30, 2015
0009 Labeling	July 14, 2015
0013 CMC Response to IR	July 30, 2015
0014 CMC Response to IR	July 31, 2015
0018 CMC Response to IR	August 25, 2015
0019 CMC Response to IR	August 15, 2015
0020 CMC Response to IR	September 22, 2015
0021 CMC Response to IR	September 24, 2015
0022 Quality Information	September 25, 2015

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Ray Frankewich	OPQ/ONDP/DNDPAPI/BI
Drug Product	Mike Adams	OPQ/ONDP/DNDPI/BII
Process	Sung Kim	OPQ/OPF/DPAIII/BVII
Microbiology	Haijing Hu	OPQ/OPF/DMA/BII
Facility	Mike Shanks	OPQ/OPF/DIA/BI
Biopharmaceutics	Banu Sizanli Zolnik	OPQ/ONDP/DB/BI
Regulatory Business Process Manager	Steven Kinsley	OMPT/CDER/OPQ/OPRO/DRBP MI/RBPMBI
Application Technical Lead	Olen Stephens	OPQ/ONDP/DNDPI/BII
ORA Lead	Paul Perdue Jr.	
Environmental Assessment (EA)	Olen Stephens	OPQ/ONDP/DNDPI/BII

Table of Contents

Table of Contents	2
Quality Review Data Sheet.....	5
Executive Summary	7
Primary Quality Review.....	13
ASSESSMENT OF THE DRUG SUBSTANCE	13
2.3.S DRUG SUBSTANCE	13
ASSESSMENT OF THE DRUG PRODUCT	19
2.3.P DRUG PRODUCT	19
R.2 Comparability Protocols.....	81
ASSESSMENT OF THE PROCESS.....	82
2.3.P DRUG PRODUCT	82
R.2 Comparability Protocols.....	115
ASSESSMENT OF THE FACILITIES.....	116
2.3.S DRUG SUBSTANCE	116
ASSESSMENT OF THE BIOPHARMACEUTICS	123
ASSESSMENT OF MICROBIOLOGY	136
P DRUG PRODUCT.....	136
P.1 Description of the Composition of the Drug Product.....	136
• Description of drug product – (32P1, p2/3).....	136
• Drug product composition – (32P1, p3/3)	136
• Description of container closure system – (33P1 p3/3 and 32P7 p4/6)	136
P.2 Pharmaceutical Development	137
P.2.5 Microbiological Attributes	137
• Container-Closure and Package integrity (CCIT) -	137
• Antimicrobial Effectiveness Testing -	138
P.3 Manufacture	138
P.3.1 Manufacturers.....	138
Site and address.....	138
Responsibility	138
Tel: 617.441.1000	138

Final drug product disposition 138
Tel: (b) (4) 138
Fill-finish drug product manufacture 138
Tel: (b) (4) 138
Packaging 138
Tel: (b) (4) 139
Endotoxin testing 138
Raw material testing 139
P.3.3 Description of the Manufacturing Process and Process Controls 139
(b) (4) MANUFACTURING PROCESS 139
• **Building and facilities (floorplan, air quality, equipment locations) - 139**
 Location of Equipment 139
• **Overall manufacturing operation (b) (4) - 140**
• **(b) (4) containers, closures, equipment and components – DMF (b) (4) was referenced for this information. 142**
• **Environmental monitoring - Information on environmental monitoring, personnel monitoring, and (b) (4) monitoring is located in DMF (b) (4). 142**
P.3.5 Process Validation and/or Evaluation 143
(b) (4) MANUFACTURING PROCESS 143
• **Drug product (b) (4) - 143**
• **(b) (4) - 145**
• **(b) (4) containers, closures, equipment and components - 147**
• **Media fill procedures and specification - 147**
• **Actions concerning product when media fills fail – (b) (4) 148**
○ **(b) (4) 148**
○ **(b) (4) 148**
○ **(b) (4) 148**
P.5 Control of Drug Product 149

P.5.1	Specification	149
P.5.2	Analytical Procedures – See P.5.1 and P.5.3	149
P.5.3	Validation of Analytical Procedures	149
•	Endotoxins	149
•	Sterility	151
P.7	Container Closure System - See P.1.	152
P.8	Stability	152
P.8.1	Stability Summary and Conclusion (32P81)	152
P.8.2	Post-Approval Stability Protocol and Stability Commitment	152
P.8.3	Stability Data	153
A	APPENDICES	153
A.2	Adventitious Agents Safety Evaluation –	153
A.2.1	Materials of Biological Origin –	153
	(b) (4)	153
R	REGIONAL INFORMATION	153
R.1	Executed Batch Record	153
R.2	Comparability Protocol – No CP was included in the application.	154
2.	REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q)	154
	MODULE 1	154
A.	PACKAGE INSERT	154
	2.3.P.7 Container/Closure System	155
A	APPENDICES	156
	ASSESSMENT OF ENVIRONMENTAL ANALYSIS	157
I.	Review of Common Technical Document-Quality (Ctd-Q) Module 1	157
	Labeling & Package Insert	157
II.	List of Deficiencies To Be Communicated - none	168
III.	Attachments	168

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS ¹	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	V		(b) (4)	Adequate	Sept. 29, 2015	
	IV		N/A			
	II		Adequate	Sept. 28, 2015		
	IV		N/A			
	IV		N/A			
	III		N/A			
	II		N/A		Supplied IH for Phase 1 / 2 clinical trials but not Phase 3 and later	
	III		N/A			
	V		N/A			
	V		N/A		Refer to micro review by Colleen Thomas 29-Oct-2009	



QUALITY ASSESSMENT



¹ Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	102799	

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
NA				

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 207793, Onivyde (irinotecan liposome injection) for intravenous infusion, is a 505(b)(2) application that references Pfizer's Camptosar (NDA 20751) for drug substance, route of administration and indication. Camptosar is dosed based on irinotecan HCl salt and the proposed drug product is dosed based on irinotecan freebase.

The submitted application is recommended for approval by the Office of Pharmaceutical Quality in that all information requests and review issues have been addressed and there are no pending approvability issues. The manufacturing and testing facilities for this NDA are deemed acceptable and an overall "approve" recommendation was entered into Panorama on September 11, 2015.

Based on the submitted stability data, a 21 month shelf-life may be granted when stored at refrigerated storage conditions (2°C–8°C) with protection from light and freezing. This includes (b) (4)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

No CMC Post-Marketing Commitments (PMC) are proposed in the application.

From a lifecycle perspective, this product is deemed a high risk product due to its liposomal formulation and method of manufacture. (b) (4) drug product manufacture, control, release and stability testing operations are conducted at Merrimack Pharmaceuticals, Inc. in Cambridge MA. (b) (4)

(b) (4) for labeling and packaging. The controls (b) (4)

(b) (4) for final drug product release are critical. In particular, the in vitro release method and acceptance criteria were negotiated throughout the review cycle. Change of this control step should be reviewed critically post-approval.

Currently, the manufacturing process allows (b) (4) (b) (4) for the final fill operations. Because of how the manufacturing process is written in the application, (b) (4) (b) (4) will require a prior approval supplement; the applicant has acknowledged this understanding. (b) (4)

(b) (4)

The application currently does not contain a validated method for (b) (4). Merrimack has committed to develop and validate a method, then submit method description and validation studies as a prior approval supplement on or before December, 2016. OPQ considers this to be a part of continual quality improvement for the manufacturing process and is not a tracked post-marketing commitment.

Similarly, to corroborate the submitted registration stability data, Merrimack has committed to perform a stability study (b) (4).

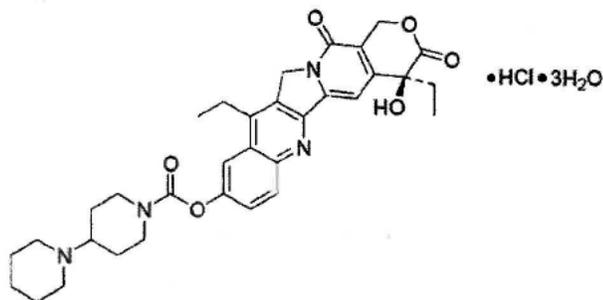
This simulates the worst case conditions for hold times prior to product distribution. This study will also incorporate light exposure conditions that simulate normal and worst case ambient light storage to demonstrate photostability. The study will be initiated on or before March 31, 2016 and will be submitted on or before May 2018. Again, this study is not a tracked post-marketing commitment

II. Summary of Quality Assessments

A. Drug Substance [Irinotecan] Quality Summary

Irinotecan is an antineoplastic agent of the topoisomerase I inhibitor class.

Irinotecan hydrochloride trihydrate, the active ingredient used to formulate Onivyde, is a water soluble synthetic camptothecin derivative with a single asymmetric center. The chemical name is (S)-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo[1H]-pyrano[3',4':6,7]-indolizino[1,2-b]quinolin-9-yl-[1,4'bipiperidine]-1'-carboxylate, monohydrochloride, trihydrate. The empirical formula is $C_{33}H_{38}N_4O_6 \cdot HCl \cdot 3H_2O$ and the molecular weight is 677.19 g/mol.



The material is a pale yellow to yellow crystalline powder which is freely soluble in DMSO and anhydrous acetic acid; and it is slightly soluble in ethanol. (b) (4)

(b) (4) The molecule has been shown to have high chemical and chiral stability.

Irinotecan hydrochloride trihydrate is manufactured by (b) (4). CMC information, including storage conditions and retest dating period, is provided by cross referenced to (b) (4) type II DMF (b) (4). This DMF was reviewed and found adequate by Dr. Raymond Frankewich (September 28, 2015).

B. Drug Product [Irinotecan Liposome Injection] Quality Summary

Onivyde (irinotecan liposome injection) for intravenous infusion is proposed for the treatment of metastatic adenocarcinoma of the pancreas, in combination with fluorouracil and leucovorin, in patients who have been previously treated with gemcitabine-based therapy.

The Onivyde liposome is a unilamellar lipid bilayer vesicle, approximately 110 nm in diameter that encapsulates an aqueous space which contains irinotecan in a gelled or precipitated state as the sucroseoctasulfate salt. The drug product liposomes are loaded with drug substance at a ratio of (b) (4) gm irinotecan/mole phospholipid. The lipid membrane is composed of phosphatidylcholine, cholesterol, and polyethyleneglycol-derivatized phosphatidylethanolamine (b) (4).

(b) (4). The liposomal components and composition were the same throughout clinical development and are the same for the proposed commercial process. As discussed above, the product strength and dose are labeled on the basis of the irinotecan freebase.

The drug product is a sterile, white to slightly yellow opaque isotonic liposomal dispersion for intravenous infusion. Each vial is intended for single dose administration only. The product is a single-dose vial containing 4.3 mg/mL of irinotecan freebase as a liposomal dispersion to deliver a maximum dose of 43 mg irinotecan freebase with an overfill of approximately (b) (4) mL to ensure that 10 mL can be withdrawn. The container closure system is a 10 mL clear type I glass vial (b) (4).

(b) (4). The stoppered vial is sealed with a non-embossed 20 mm flip-off overseal.

The appropriate dose of drug product is intended to be admixed into 500 cc of 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP for administration by intravenous infusion over 90 minutes. Based on in-use stability study data, the admixed solution may be held for up to 24 hours when stored at 2-8°C without freezing and for up to 4 hours when stored at ambient temperature (approximately 25°C). The healthcare provider should allow diluted solution to come to room temperature prior to administration.

Manufacture of Phase 3 clinical material (by the Phase 3 process) occurred at the same scale as the commercial process. The manufacturing process is (b) (4) performed by Merrimack Pharmaceuticals. (b) (4) step is performed by (b) (4). Label-packaging steps are performed by (b) (4)

The proposed commercial target batch size is (b) (4) which obtains (b) (4) vials. No (b) (4) are proposed. (b) (4) The (b) (4) manufacturing steps have been identified as having Critical Process Parameters (CPPs) which have the potential to affect the drug product Critical Quality Attributes (CQAs). (b) (4)

(b) (4)

(b) (4) Additional parameters have been identified as process controls, but have been shown not to affect CQAs in the verified ranges.

The drug product is sterile. USP Sterility <71>, (b) (4) is performed for drug product release. Container closure integrity is performed in stability studies in lieu of sterility.

The submitted stability data supports an initial shelf life of 21 months with storage at refrigerated storage conditions (2°C–8°C) and protection from light and freezing. This includes (b) (4)

(b) (4)

Negotiations of the information in the labels and labeling are on-going, including the designation of strength by the freebase rather than the hydrochloride salt.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Onivyde
Non Proprietary Name of the Drug Product	Irinotecan liposome solution
Non Proprietary Name of the Drug Substance	Irinotecan
Proposed Indication(s) including Intended Patient Population	ONIVYDE (irinotecan liposome injection) is indicated for the treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and leucovorin, in patients who have been previously treated with gemcitabine.

Duration of Treatment	Until disease progression
Maximum Daily Dose	70 mg/m ²
Alternative Methods of Administration	NA

D. Biopharmaceutics Considerations

The in vitro release method and final acceptance criteria are acceptable for quality control purposes.

In vitro release method: [REDACTED] (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Final in vitro release acceptance criteria:

2 hrs: [REDACTED] (b) (4) %

4 hrs: [REDACTED] (b) (4) %

16 hrs: NLT [REDACTED] (b) (4) %

The Division of Biopharmaceutics recommends approval of NDA 207793 for Irinotecan Liposomal Suspension, 4.3 mg/mL.

E. Novel Approaches

F. Any Special Product Quality Labeling Recommendations

Note the discussion above for the reasoning to label this produce on the strength of the irinotecan free base and to *not* include a salt equivalence statement.

G. Life Cycle Knowledge Information (see Attachment A)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead's Note: Throughout the review, since the strength designation has not been completed with the applicant, review sections will either refer to the strength as 50 mg of the irinotecan hydrochloride trihydrate or 43 mg irinotecan. Similarly, the strength of the solution is expressed as either 5 mg/mL irinotecan hydrochloride trihydrate or 4.3 mg/mL irinotecan. OPQ's recommendation is to label on the basis of the irinotecan freebase.

ASSESSMENT OF THE BIOPHARMACEUTICS

37. Are the in-vitro dissolution test and acceptance criteria adequate for assuring quality control and consistent bioavailability of the drug product?

The in vitro release test and acceptance criteria assure the quality control of the proposed drug product.

a. What are the highlights of the chemistry and physico-chemical properties of the drug substance (e.g. solubility) and formulation of the drug product?

Irinotecan hydrochloride trihydrate is freely soluble in DMSO, and anhydrous acetic acid, and slightly soluble in ethanol. The drug product liposome is a small unilamellar lipid bilayer vesicle, approximately 110 nm in diameter, encapsulates irinotecan in a gelated or precipitated stated as sucrosofate salt in the aqueous space of the liposome. Refer to the drug substance and drug product section of this review for additional details on the description of the drug product and the physico-chemical properties of irinotecan.

b. What is the proposed in vitro release method?

The in vitro release method measures the amount of irinotecan released from the internal environment of the liposome over time. (b) (4)

[REDACTED]

(b) (4)
[REDACTED] impact the in vitro release method. Therefore, the methods are described briefly below; however adequacies of these methods and acceptance criteria are reviewed under the Drug Product section of this review.

[REDACTED] (b) (4)



(b) (4)

- c. What data are provided to support the adequacy of the proposed in vitro release method (e.g. medium, apparatus selection, etc.)?

Regulatory History: During the pre-NDA Type B meeting (September 12, 14), the Applicant was requested to improve the in vitro release method (b) (4). In this original submission, the Applicant re-developed the in vitro release method (b) (4) which resulted in drug release greater than (b) (4)% of label claim.



(b) (4)

(b) (4)

d. What information is available to support the robustness (e.g. linearity, accuracy, etc.) of the in vitro release methodology?

The in vitro release method was validated for accuracy, precision (repeatability and intermediate precision), linearity, range, specificity, robustness and solution stability according to ICH guidelines. (Refer to the link for detailed information <\\cdsesub1\evsprod\nda207793\0008\m3\32-body-data\32p-drug-prod\irinotecan-liposome-injection-injectable-5-mg-ml-01\32p5-contr-drug-prod\32p53-val-analyt-proc\32p5312.pdf>)

e. What data are available to support the discriminating power of the method?

The Applicant tested the discriminating ability of the in vitro release method (b) (4) by intentionally manufacturing defective liposomes. As shown in the Table below, the Applicant (b) (4) The Applicant used the commercial lot as the control.

Table 2: Generation of Defective MM-398 Liposomes

Experiment Number	Experiment Description	Expected Outcome
1		(b) (4)
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		

Drug release profiles of the liposomes intentionally manufactured as defective and its controls are shown below.

Table 3: % Release of Irinotecan for Manufactured Defective Liposomes and Approved Lots of MM-398

(b) (4)



Table 7: IVR Release Timepoint Results Summary and Difference/Similarity Factors of Approved Lots and Manufactured Defective Batches of MM-398

(b) (4)



Reviewer's Assessment:

The in vitro release method and the final acceptance criteria (2 hr: (b) (4)%, 4 hr: (b) (4)%, and 16 hr: NLT (b) (4)%) discriminates against the defective liposomes manufactured for experiments, 2, 6, 7, 8, 9, 10 and 12. Although, the in vitro release method and acceptance criteria are not sensitive to the changes (b) (4), the presence of (b) (4) is related to (b) (4) and it is controlled directly or indirectly by the other analytical methods.

f. Is the proposed in vitro release method bio-relevant? What data are available to support this claim?

No, the method is not bio-relevant.

g. Is the proposed method acceptable? If not, what are the deficiencies?

Yes, the in-vitro release method is acceptable.

h. What are the proposed in vitro release acceptance criteria for this product?

Proposed Dissolution Acceptance Criteria for Irinotecan liposome injection	
2 hr:	(b) (4) %
4 hr:	(b) (4) %
16 hr:	greater than (b) (4) %

i. What data are available to support these criteria?

The Applicant provided in vitro release data of four process performance qualification (PPQ) lots. The Applicant also provided in vitro release data of the aged Phase 3 and primary stability batches as shown below. The reason for using the aged phase 3 and primary stability batches is that the method was modified to achieve greater than (b) (4) % of the labeled drug claim.

2 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)



Table 16: In Vitro Drug Release Data Range and Acceptance Criteria

	Phase 1 & 2	Phase 3 & Primary Stability Batches	Data Range for Phase 3, Primary Stability, clinical, and PPQ Batches	Proposed Commercial
<i>In Vitro</i> Drug Release	Not Tested	Report (b) (4)	(b) (4), % at 2 hrs % at 4 hrs % at 16 hrs	(b) (4), % at 2 hrs % at 4 hrs % at 16 hrs

Reviewer's Assessment:

There was no stability trends observed between the PPQ lots (between 4-6 months) and the aged samples (between 24-45 months) ranging from approximately 5 months up to 45 months.

- j. Are the acceptance criteria acceptable? If not, what are the recommended criteria? Is the setting of the dissolution acceptance criteria based on data from clinical and registration batches? If not, is the setting based on BE or IVIVC data?

The Applicant's proposed acceptance criteria are not acceptable. It is not FDA's practice to accept in-vitro drug release acceptance ranges based on \pm SD for all dosage forms. The Applicant's proposed acceptance criteria are permissive and

will allow all the defective liposomal formulations used to investigate the discriminating power of the in vitro release method as shown below (red shows that failed time points with FDA recommended acceptance criteria)



(b) (4)

Time (hrs)	Applicant proposed	FDA recommended
2.0		(b) (4)
4.0		
16.0		
Discriminating ability		

Based on the analysis above, the IR comment below was sent to the Applicant via email prior to a teleconference.

IR Comment conveyed to the Applicant dated 9/18/2015

The proposed dissolution acceptance criteria are not supported by the data in the Application. Based on the in vitro performance of the PPQ, aged Phase 3, and clinical stability batches, FDA recommends the following in-vitro release acceptance criteria:

2 hrs: (b) (4) %
 4 hrs: (b) (4) %
 16 hrs: NLT (b) (4) %

T-Con with the Applicant dated 9/18/2015

During the t-con, the FDA re-iterated that the Applicant’s acceptance criteria are permissive and not supported by the data, and is not acceptable. In conclusion, the Applicant stated that (b) (4)

(b) (4) however, the Applicant stated that they would re-evaluate their proposed acceptance criteria, and submit an amendment.

The Applicant’s response in an amendment S-0020 dated 9/20/2015

The Applicant proposed the new acceptance criteria below based on ±2.5 SD based on a total of 14 batches (two additional batches along with the previous batch data).

Table 1: Comparison of IVR Specification Ranges: Original, FDA Proposed, and New Merrimack Proposed Ranges

IVR Test Sampling Time Point	Original NDA on n=12	New FDA Proposal	New Proposed 2.5 SD on n=14
2hr	(b) (4)	(b) (4)	(b) (4)
4hr	(b) (4)	(b) (4)	(b) (4)
16hr	(b) (4)	(b) (4)	(b) (4)

Table 2: IVR Release Data from Application Updated with 2 Additional Batches

Lot No.	% Released Drug at 2 hours	% Released Drug at 4 hours	% Released Drug at 16 hours
1-FIN-1221	(b) (4)	(b) (4)	(b) (4)
1-FIN-1220	(b) (4)	(b) (4)	(b) (4)
1-FIN-1515	(b) (4)	(b) (4)	(b) (4)
1-FIN-1562	(b) (4)	(b) (4)	(b) (4)
1-FIN-1637	(b) (4)	(b) (4)	(b) (4)
3-FIN-1780	(b) (4)	(b) (4)	(b) (4)
3-FIN-1781	(b) (4)	(b) (4)	(b) (4)
3-FIN-1782	(b) (4)	(b) (4)	(b) (4)
3-FIN-2092	(b) (4)	(b) (4)	(b) (4)
3-FIN-2062	(b) (4)	(b) (4)	(b) (4)
3-FIN-2063	(b) (4)	(b) (4)	(b) (4)
3-FIN-2064	(b) (4)	(b) (4)	(b) (4)
(new batch) 150163	(b) (4)	(b) (4)	(b) (4)
(new batch) 150164	(b) (4)	(b) (4)	(b) (4)
New n=14 Average	(b) (4)	(b) (4)	(b) (4)
New n=14 SD	(b) (4)	(b) (4)	(b) (4)
New n=14 Ave-2.5SD	(b) (4)	(b) (4)	(b) (4)
New n=14 Ave+2.5SD	(b) (4)	(b) (4)	(b) (4)
Initially filed average (n=12)	(b) (4)	(b) (4)	(b) (4)
SD of filed data (n=12)	(b) (4)	(b) (4)	(b) (4)

Note: Red text indicates data from application that would be OOS or edge of failure using FDA's proposed ranges.

Reviewer's Assessment:

The Applicant's justification for minimum batch variability does not hold. In general, FDA not only considers intra-batch variability but also inter-batch variability. The Applicant's proposal based on ± 2.5 SD is not acceptable and the IR below was sent to the Applicant on 9/25/2015.

IR Comment conveyed to the Applicant dated 9/25/2015

The FDA has reviewed your response to the Information Request; the provided revision of the proposed in-vitro release acceptance criteria is not acceptable. It is not FDA's practice to recommend or accept in-vitro drug release acceptance ranges based on $\pm SD$ for all dosage forms, including liposomal suspensions for injection. Based on the totality of the data submitted, including those for two new batches, FDA recommends the following in-vitro release acceptance criteria for batch release and stability testing (based on Level 2 testing; the means should be within the ranges at 2 and 4 h):

- 2 h: (b) (4) %
- 4 h: (b) (4) %
- 16 h: (b) (4) %

Update the Specifications table with the above recommended in-vitro release acceptance criteria.

The Applicant's response in an amendment S-0022 dated 9/25/2015

The Applicant agreed to FDA's recommendation as shown below.

Final in vitro release acceptance criteria	
2 hrs:	(b) (4) %
4 hrs:	(b) (4) %
16 hrs:	NLT (b) (4) %

38. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

The same formulation was used throughout the clinical development and for commercial use. The only change was (b) (4)

Reviewer's Assessment:

The in vitro release method and final acceptance criteria are acceptable for quality control purposes.

(b) (4)

Final in vitro release acceptance criteria:

2 hrs: (b) (4) %
 4 hrs: (b) (4) %
 16 hrs: NLT (b) (4) %



**OVERALL ASSESSMENT AND SIGNATURES:
BIOPHARMACEUTICS**

Reviewer's Assessment and Signature:

The Division of Biopharmaceutics recommends APPROVAL of NDA 207793 for Irinotecan Liposomal Injection.

Banu Zolnik, Ph.D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

Secondary Review Comments and Concurrence:

I concur with Dr. Zolnik's assessment and approval recommendation for NDA 207793.

Okpo Eradiri, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

ASSESSMENT OF MICROBIOLOGY

39. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

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)

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)	(b) (4)
Seal	20 mm aluminum flip off seal with white plastic cap	(b) (4)

Acceptable

P.2 Pharmaceutical Development**P.2.5 Microbiological Attributes**

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

(b) (4)



(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

Applicant's Response:

Reviewer's Assessment: The NDA is adequate in support of the (b) (4) manufacturing for the subject drug product.

2.3.P.7 Container/Closure System

40. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Applicant's Response:

Reviewer's Assessment: Container/closure system was evaluated in Question 39.

A APPENDICES**A.2 Adventitious Agents Safety Evaluation**

41. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response:

Reviewer's Assessment: NA, there are no adventitious agents.

42. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response:

Reviewer's Assessment: NA

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature: This NDA is recommended for approval from a quality microbiology perspective.

Denise A. Miller
Microbiologist, OPF/DMA/Branch II
09/30/15

Secondary Review Comments and Concurrence: I concur with Denise Miller's Product Quality Microbiology assessment and approval recommendation for NDA 207793.

Neal J. Sweeney, Ph.D.
Microbiology Quality Assessment Lead
OPQ/OPF/DMA/Branch II

9/30/15

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

43. Is the applicant's claim for categorical exclusion acceptable? Yes.
44. Is the applicant's Environmental Assessment adequate for approval of the application? NA

Applicant's Response:

Reviewer's Assessment: Merrimack Pharmaceuticals, Inc. is requesting a categorical exclusion from the preparation of an environmental assessment (EA) for irinotecan liposome injection, 4.3 mg/mL, according to section 505(b) of the Federal Food, Drug, and Cosmetic Act. No extraordinary circumstances exist, as referenced in 21 CFR 25.21(a). The approval of this will increase the use of the irinotecan active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion. The applicant's claim of a categorical exclusion as per 21 CFR 25.31(b) is granted.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature: Request for exemption is granted.

Secondary Review Comments and Concurrence: Olen Stephens, Ph.D.

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1**Labeling & Package Insert**

Note from the ATL: Labeling negotiations are on-going through the clinical division with the applicant. The version below represents the current recommendations at the time of this review and likely will change as negotiations proceed. For example, the applicant has not agreed to the strength representation based on the irinotecan freebase, so numerical values of strength may be modified.

- 1. Package Insert (Amendment S-019)**
 - (a) "Highlights" Section (21CFR 201.57(a))****HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all of the information needed to use ONIVYDE™ safely and effectively. See full prescribing information for ONIVYDE™

ONIVYDE™ (irinotecan liposome injection) for intravenous infusion
Initial U.S. Approval: 1996

[black box warning]

INDICATIONS AND USAGE

ONIVYDE is a topoisomerase 1 inhibitor indicated (b) (4)
[redacted] (1)

DOSAGE AND ADMINISTRATION

- * Do not substitute ONIVYDE for or with other (b) (4), (2.1)
- * (b) (4)
- * ONIVYDE (b) (4) mg/m² intravenous infusion over 90 minutes, every 2 weeks, (b) (4)
[redacted]
- * [redacted] (b) (4)

DOSAGE FORMS AND STRENGTHS

Injection: 43 mg/10 mL in a single (b) (4) dose vial

CONTRAINDICATIONS

(b) (4)

WARNINGS AND PRECAUTIONS

[redacted] (b) (4)

- * Interstitial Lung Disease: Fatal interstitial (b) (4) disease (b) (4) occurred in patients receiving irinotecan HCl. Discontinue ONIVYDE if (b) (4) is diagnosed (5.5)
- * Embryofetal Toxicity: (b) (4) can cause harm (b) (4)

[redacted]

[redacted] (b) (4)



QUALITY ASSESSMENT



Revised: XX/2015

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	ONIVYDE™ (irinotecan liposome injection)	Acceptable
Dosage form, route of administration	for intravenous infusion	Acceptable, except that (b) (4) should be revised to "single dose vial".
Controlled drug substance symbol (if applicable)		N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Solution for IV infusion, 4.3 mg/mL irinotecan freebase	Acceptable

Conclusion:

Acceptable for CMC except for the values for strength and dosage. After discussion the clinical team concluded that the maximum dose should be listed in the package insert as 70 mg/m² (80 mg/m² HCl salt converts to 69 mg/m² freebase). The proposed revisions will be sent to the applicant and resolved as part of the labeling negotiations.

(b) "Full Prescribing Information" Section

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

[Black Box Warning]

1 INDICATIONS AND USAGE

ONIVYDE™ (b) (4) is indicated (b) (4)

2 DOSAGE AND ADMINISTRATION

2.1 (b) (4)

Important Use Information

DO NOT SUBSTITUTE ONIVYDE for or with other drug (b) (4) containing irinotecan.

(b) (4)

Recommended Dose

Administer ONIVYDE (b) (4) mg/m² intravenously over 90 minutes, (b) (4)

(b) (4) every 2 weeks.

(b) (4)

Premedication

(b) (4)

2.2 Dose Modifications for Adverse Reactions

(b) (4)

Table 1: Recommended Dose Modifications for ONIVYDE

(b) (4)

(b) (4)

(b) (4)

2.3 Preparation and Administration

ONIVYDE is a cytotoxic drug. Follow applicable special handling and disposable procedures.¹

Preparation

(b) (4)

Administration

Do not use any in-line filters. Discard any unused portion.

3 DOSAGE FORMS AND STRENGTHS

Injection: 43 mg/10 mL (b) (4) irinotecan (b) (4) base, in a single (b) (4) dose vial

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Solution for IV infusion	Acceptable
Strengths: in metric system	mg/mL	Acceptable
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.		See section 11

Conclusion:

Sections 2.1 & 2.2: Route of administration and need to dilute are acceptable. Dose to be revised by ClinPharm; max dose to be listed as 70 mg/m².

Section 2.3: Special handling statement is acceptable. Dose preparation description is complete and storage statements are supported by studies in NDA section 3.2.P.2.6. The non-use of filter is acceptable to clinical and microbiology.

Section 3: Description is correct except that strength statement and '(b) (4)' need to be corrected.

#11: Description (21CFR 201.57(c)(12))**11 DESCRIPTION**

ONIVYDE (b) (4) is a topoisomerase inhibitor (b) (4) for intravenous use. ONIVYDE is (b) (4) a sterile, white to slightly yellow opaque isotonic liposomal dispersion (b) (4). Each 10 mL vial contains 43 mg irinotecan (b) (4) base at a concentration of 4.3 mg/mL.

The chemical name of irinotecan is (S)-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo1H-pyrano[3',4':6,7]-indolizino[1,2-b]quinolin-9-yl-[1,4'bipiperidine]-1'-carboxylate. The empirical formula is C₃₃H₃₈N₄O₆ and the molecular weight is (b) (4).

The (b) (4) liposome is a (b) (4) unilamellar lipid bilayer vesicle, approximately 110 nm in diameter, which encapsulates an aqueous space (b) (4) irinotecan in a gelated or precipitated state, as the sucrooctasulfate salt. (b) (4) are composed of 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), 6.81 mg/mL; cholesterol, 2.22 mg/mL; and methoxy-terminated polyethylene glycol (MW 2000)-distearoylphosphatidylethanolamine (MPEG-2000-DSPE), 0.12 mg/mL. Each mL also contains 2-[4-(2-hydroxyethyl) piperazin-1-yl]ethanesulfonic acid (HEPES) as a buffer, 4.05 mg/mL; sodium chloride as isotonicity reagent, 8.42 mg/mL. (b) (4)

15 REFERENCES

OSHA Hazardous Drugs. *OSHA*. <http://www.osha.gov/SLTC/hazardousdrugs/index.html>

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name		Acceptable
Dosage form and route of administration		Acceptable
Active moiety expression of strength with equivalence statement for salt (if applicable)		Acceptable
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	All liposome and solution ingredients are listed quantitatively	Acceptable
Statement of being sterile (if applicable)	Sterile	Acceptable
Pharmacological/ therapeutic class		Acceptable
Chemical name, structural formula, molecular weight		Acceptable
If radioactive, statement of important nuclear characteristics.		N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)	[H and liposome diameter	Acceptable

Conclusion:

Section 11: Strength statement is to be revised. Acceptable for product description, API chemical name/MW, liposome description/size/components, and dosage solution composition.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

ONIVYDE is available as a single (b)(4) dose 43 mg (b)(4) NDC: 69171-398-01

Storage and Handling

(b)(4) ONIVYDE at 2°C to 8°C (36°F to 46°F). Do NOT freeze. Protect from light.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	4.3 mg/mL freebase	Acceptable
Available units (e.g., bottles of 100 tablets)	10cc glass vial	Acceptable
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	appearance	Acceptable based on information in ND A section 3.2.P.5.1
Special handling (e.g., protect from light, do not freeze)	Protect from light, do not freeze	Acceptable based on data in NDA section 3.2.P.2.6
Storage conditions	2-8°C	Acceptable based on data in NDA section 3.2.P.8



QUALITY ASSESSMENT



Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Drug product manufacturing site	Acceptable based on information in NDA section 3.2.P.3.1

Manufactured (b) (4)
Merrimack Pharmaceuticals, Inc.
Cambridge, MA 02139
ONIVYDE is a trademark of Merrimack Pharmaceuticals, Inc.

Conclusion:
Section 16: NDC is provided. Revise strength and “(b) (4)” statements. Storage statement is supported by NDA section 3.2.P.8. “Manufactured (b) (4)” statement is supported by NDA section 3.2.P.3.1.

2. Container and Carton Labeling

1) Immediate Container Label (Amendment S-019)



(b) (4)

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Onivyde (irinotecan liposome injection); font size addressed by DMEPA	Acceptable
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	4.3 mg/mL freebase	Acceptable
Route of administration (21.CFR 201.100(b)(3))	Solution for IV infusion	Acceptable
Net contents* (21 CFR 201.51(a))	43 mg/10 mL	Acceptable
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Provided in package insert; not enough room on this label	Acceptable
Lot number per 21 CFR 201.18	Provided	Acceptable
Expiration date per 21 CFR 201.17	Provided	Acceptable
“Rx only” statement per 21 CFR 201.100(b)(1)	Provided	Acceptable
Storage (not required)	Store at 2-8oC; protect from light and freezing	Acceptable
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	Acceptable
Bar Code per 21 CFR 201.25(c)(2)***	Provided on carton label	Acceptable
Name of manufacturer/distributor (21 CFR 201.1)	Provided	Acceptable based on NDA section 3.2.P.3.1
Others		N/A

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled “sample”, “physician’s sample”, or a substantially similar statement and the contents of the package do not exceed 8 grams.

**For solid oral dosage forms, CDER policy provides for exclusion of “oral” from the container label

***Not required for Physician’s samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: Acceptable with changes of (b) (4) to “single dose” vial and representation of strength to the irinotecan freebase.

2) Carton Labeling (Amendment S-019)



QUALITY ASSESSMENT



(b) (4)



QUALITY ASSESSMENT



Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Onivyde (irinotecan liposome injection); font size addressed by DMEPA	Acceptable
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	4.3 mg/mL	Acceptable
Net contents (21 CFR 201.51(a))	43 mg/mL	Acceptable
Lot number per 21 CFR 201.18	Provided	Acceptable
Expiration date per 21 CFR 201.17	Provided	Acceptable
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	Quantitative list is provided	Acceptable based on NDA section 3.2.P,1
Sterility Information (if applicable)	Sterile	Acceptable
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Provided	Acceptable
Storage Conditions	Store at 2-8°C; protect from light and freezing	Acceptable
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	Acceptable
Bar Code per 21 CFR 201.25(c)(2)**	Provided	Acceptable
Name of manufacturer/distributor	Provided	Acceptable
"See package insert for dosage information" (21 CFR 201.55)	Provided	Acceptable
"Keep out of reach of children" (optional for Rx, required for OTC)	Not present	Acceptable
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))	Solution for IV infusion	Acceptable

Conclusion:

Acceptable except that statement "(b) (4)" should be revised to "single dose vial" and representation of strength to the irinotecan freebase.

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:

The CMC information is acceptable; final label negotiations are on-going.

William M. Adams, Review Chemist
OPQ/ONDP/DNDP/Branch II
September 30, 2015

Secondary Review Comments and Concurrence:

Olen Stephens, Acting Branch Chief
OPQ/ONDP/DNDP/Branch II
September 30, 2015

II. List of Deficiencies To Be Communicated - none**III. Attachments****A. Lifecycle Knowledge Management**



QUALITY ASSESSMENT



PRODUCT PROPERTY//IMPACT OF CHANGE/CQAS	CHANGES & VARIATIONS	FAILURE MODE	INITIAL RISK SCORE	FINAL RISK SCORE	LIFECYCLE CONSIDERATIONS
Sterility	<ul style="list-style-type: none"> • Formulation • Container closure • Process parameters • Scale/equipments • Site 	• Non-sterile unit(s)	HIGH	HIGH	(b) (4)
Endotoxin Pyrogen	<ul style="list-style-type: none"> • Formulation • Container closure • Process parameters • Scale/equipments • Site 	• Excessive Endotoxin Levels	MEDIUM	MEDIUM	
Assay (API), stability	<ul style="list-style-type: none"> • Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site 	(b) (4)	LOW	LOW	
Uniformity of Dose (Fill Volume/deliverable volume)	<ul style="list-style-type: none"> • Formulation • Container closure • Process parameters • Scale/equipments • Site 	• Insufficient dose	LOW	LOW	
Osmolality	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipments • Site 	<ul style="list-style-type: none"> • Irritation • Edema 	LOW	LOW	
pH- (Low)	<ul style="list-style-type: none"> • Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site 	• Irritation	LOW	LOW	



QUALITY ASSESSMENT



PRODUCT PROPERTY/IMPACT OF CHANGE/CQAS	CHANGES & VARIATIONS	FAILURE MODE	INITIAL RISK SCORE	FINAL RISK SCORE	LIFECYCLE CONSIDERATIONS
Particle size distribution (suspension)	<ul style="list-style-type: none"> • Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site 	<ul style="list-style-type: none"> • Bioavailability • Embolism 	MEDIUM	MEDIUM	(b) (4)
Particulate matter (non aggregate for solution only)	<ul style="list-style-type: none"> • Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site 	<ul style="list-style-type: none"> • Irritation • Embolism 	MEDIUM	MEDIUM	
Leachable extractables	<ul style="list-style-type: none"> • Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site 	<ul style="list-style-type: none"> • Generation of impurities 	LOW	LOW	
Appearance (Color/turbidity)	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipments • Site 	<ul style="list-style-type: none"> • Degradation 	LOW	LOW	
<i>In vitro</i> Release	<ul style="list-style-type: none"> Formulation Stability Manufacturing Process 	<ul style="list-style-type: none"> Bioavailability Potency 	Not evaluated	MEDIUM	(b) (4)



QUALITY ASSESSMENT



Task Summary Task Details Issues Task Email Form Updates Application History **Inspection Management Form**

Inspection Management Form

Apr 29, 2015

Inspection Management Form

NDA 207793-Orig1-Form 3674 - New/NDA(3)

- (b) (4) CTL CONTROL TESTING LABORATORY | Approve Facility ▾
- (b) (4) CTL CONTROL TESTING LABORATORY | Approve Facility ▾
- (b) (4) CTL CONTROL TESTING LABORATORY | Approve Facility ▾
- (b) (4) CTL CONTROL TESTING LABORATORY | Approve Facility ▾
- (b) (4) CTL CONTROL TESTING LABORATORY | Approve Facility ▾
- (b) (4) SVS STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS | Approve Facility ▾
- (b) (4) SVS STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS | Approve Facility ▾
- (b) (4) CSN NON-STERILE API BY CHEMICAL SYNTHESIS | Approve Facility ▾
- HERRINACK PHARMACEUTICALS, INC. | 3008532848 (b) (4) Approve Facility ▾
- (b) (4) FACILITY PROFILE CANCELLED ▾
- (b) (4) FACILITY PROFILE CANCELLED ▾
- HERRINACK PHARMACEUTICALS, INC. | 3008532848 (b) (4) FACILITY PROFILE CANCELLED ▾
- HERRINACK PHARMACEUTICALS, INC. | 3008532848 | SVS STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS - FACILITY PROFILE CANCELLED ▾
- (b) (4) FACILITY PROFILE CANCELLED ▾

Overall Manufacturing Inspection Recommendation

- Approve
- Withhold

OPF Reviewer

Michael Shanks
Assign

IM - OPF Reviewer

Edit Assignment

This was done on
Sep 11, 2015
(17 mins ago)

Status
Complete

Requested by
 DARRTS Integration

The status is waiting on
in Facilities

Last Update: **Sep 11, 2015** Submitted On: **Apr 29, 2015**

Reference Number:
4498055

Application #: 207793 Submission Type: 505 (b)(2)

Established/Proper Name:
Irinotecan Liposome/
Onivyde

Applicant: Merrimack
Pharmaceuticals, Inc. Letter Date: 12/26/2014

Dosage Form: Injection

Chemical Type: Stamp Date: 4/30/2015

Strength: 5mg/mL

A. FILING CONCLUSION				
	Parameter	Yes	No	Comment
1.	DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?	Yes		The proposed indication" the treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil (5-FU) and leucovorin (LV), in patients previously treated with gemcitabine."
2.	If the application is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			Will be discussed at the internal Kick off meeting
3.	Are there any potential review issues to be forwarded to the Applicant, not including any filing comments stated above?		No	Describe potential review issues here or on additional sheets

B. NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
Product Type				
1.	New Molecular Entity ¹	<input type="checkbox"/>	X	
2.	Botanical ¹	<input type="checkbox"/>	X	
3.	Naturally-derived Product	<input type="checkbox"/>	X	(b) (4)
4.	Narrow Therapeutic Index Drug	X	<input type="checkbox"/>	
5.	PET Drug	<input type="checkbox"/>	X	
6.	PEPFAR Drug	<input type="checkbox"/>	X	
7.	Sterile Drug Product	X	<input type="checkbox"/>	
8.	Transdermal ¹	<input type="checkbox"/>	X	
9.	Pediatric form/dose ¹	<input type="checkbox"/>	X	
10.	Locally acting drug ¹	<input type="checkbox"/>	X	
11.	Lyophilized product ¹	<input type="checkbox"/>	X	
12.	First generic ¹	<input type="checkbox"/>	X	
13.	Solid dispersion product ¹	<input type="checkbox"/>	X	
14.	Oral disintegrating tablet ¹	<input type="checkbox"/>	X	
15.	Modified release product ¹	<input type="checkbox"/>	X	
16.	Liposome product ¹	X	<input type="checkbox"/>	
17.	Biosimilar product ¹	<input type="checkbox"/>	X	
18.	Combination Product	<input type="checkbox"/>	X	
19.	Other	<input type="checkbox"/>	X	

Regulatory Considerations					
20.	USAN Name Assigned		<input checked="" type="checkbox"/>	<input type="checkbox"/>	
21.	End of Phase II/Pre-NDA Agreements		<input checked="" type="checkbox"/>	<input type="checkbox"/>	Rolling submission for CMC
22.	SPOTS (Special Products On-line Tracking System)		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
24.	Comparability Protocol(s) ²		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
25.	Other		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Quality Considerations					
26.	Drug Substance Overage		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
27.	Design Space	Formulation	<input type="checkbox"/>	<input type="checkbox"/>	
28.		Process	<input type="checkbox"/>	<input type="checkbox"/>	
29.		Analytical Methods	<input type="checkbox"/>	<input type="checkbox"/>	
30.		Other	<input type="checkbox"/>	<input type="checkbox"/>	
31.	Real Time Release Testing (RTRT)		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
32.	Parametric Release in lieu of Sterility Testing		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
33.	Alternative Microbiological Test Methods		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
34.	Process Analytical Technology ¹		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	<input type="checkbox"/>	<input type="checkbox"/>	
36.		Excipients	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
37.		Microbial	<input type="checkbox"/>	<input type="checkbox"/>	
38.	Unique analytical methodology ¹		<input checked="" type="checkbox"/>	<input type="checkbox"/>	Vitro release test method
39.	Excipients of Human or Animal Origin		<input checked="" type="checkbox"/>	<input type="checkbox"/>	
40.	Novel Excipients		<input checked="" type="checkbox"/>	<input type="checkbox"/>	
41.	Nanomaterials ¹		<input checked="" type="checkbox"/>	<input type="checkbox"/>	Discussion is needed
42.	Hold Times Exceeding 30 Days		<input type="checkbox"/>	<input type="checkbox"/>	
43.	Genotoxic Impurities or Structural Alerts		<input checked="" type="checkbox"/>	<input type="checkbox"/>	
44.	Continuous Manufacturing		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
45.	Other unique manufacturing process ¹		<input checked="" type="checkbox"/>	<input type="checkbox"/>	Liposome DP
46.	Use of Models for Release (IVIVC, dissolution models for real time release).		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
47.	New delivery system or dosage form ¹		<input checked="" type="checkbox"/>	<input type="checkbox"/>	
48.	Novel BE study designs		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
49.	New product design ¹		<input checked="" type="checkbox"/>	<input type="checkbox"/>	
50.	Other		<input type="checkbox"/>	<input checked="" type="checkbox"/>	

¹Contact Office of Testing and Research for review team considerations

²Contact Post Marketing Assessment staff for review team considerations

C. FILING CONSIDERATIONS					
	Parameter	Yes	No	N/A	Comment
GENERAL/ADMINISTRATIVE					
1.	Has an environmental assessment report or categorical exclusion been provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? <input type="checkbox"/> Drug Substance <input type="checkbox"/> Drug Product <input type="checkbox"/> Appendices <input type="checkbox"/> Facilities and Equipment	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

C. FILING CONSIDERATIONS				
	<ul style="list-style-type: none"> ○ Adventitious Agents Safety Evaluation ○ Novel Excipients □ Regional Information <ul style="list-style-type: none"> ○ Executed Batch Records ○ Method Validation Package ○ Comparability Protocols 			
FACILITY INFORMATION				
3.	<p>Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list:</p> <ul style="list-style-type: none"> □ Name of facility, □ Full address of facility including street, city, state, country □ FEI number for facility (if previously registered with FDA) □ Full name and title, telephone, fax number and email for on-site contact person. □ Is the manufacturing responsibility and function identified for each facility, and □ DMF number (if applicable) 	X	<input type="checkbox"/>	<input type="checkbox"/>
				See DS information for (b) (4) DS reviewer will need to confirm other DMF is used for the commercial DP
4.	<p>Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA:</p> <ul style="list-style-type: none"> □ Is a manufacturing schedule provided? □ Is the schedule feasible to conduct an inspection within the review cycle? 	X	<input type="checkbox"/>	<input type="checkbox"/>
DRUG SUBSTANCE INFORMATION				
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	X	<input type="checkbox"/>	<input type="checkbox"/>
6.	<p>Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review?</p> <ul style="list-style-type: none"> □ general information □ manufacture <ul style="list-style-type: none"> ○ Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) ○ Includes descriptions of changes in the 	X	<input type="checkbox"/>	<input type="checkbox"/>

C. FILING CONSIDERATIONS

	<p>manufacturing process from material used in clinical to commercial production lots – BLA only</p> <ul style="list-style-type: none"> ○ Includes complete description of product lots and their uses during development – BLA only <ul style="list-style-type: none"> <input type="checkbox"/> characterization of drug substance <input type="checkbox"/> control of drug substance <ul style="list-style-type: none"> ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only <input type="checkbox"/> reference standards or materials <input type="checkbox"/> container closure system <input type="checkbox"/> stability <ul style="list-style-type: none"> ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment 				
--	---	--	--	--	--

DRUG PRODUCT INFORMATION

7.	<p>Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review?</p> <ul style="list-style-type: none"> <input type="checkbox"/> Description and Composition of the Drug Product <input type="checkbox"/> Pharmaceutical Development <ul style="list-style-type: none"> ○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots ○ Includes complete description of product lots and their uses during development <input type="checkbox"/> Manufacture <ul style="list-style-type: none"> ○ If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter? <input type="checkbox"/> Control of Excipients <input type="checkbox"/> Control of Drug Product <ul style="list-style-type: none"> ○ Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) ○ Includes data to demonstrate comparability 	X	<input type="checkbox"/>	<input type="checkbox"/>	
----	--	---	--------------------------	--------------------------	--

C. FILING CONSIDERATIONS					
	<p>of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred)</p> <ul style="list-style-type: none"> ○ Analytical validation package for release test procedures, including dissolution □ Reference Standards or Materials □ Container Closure System <ul style="list-style-type: none"> ○ Include data outlined in container closure guidance document □ Stability <ul style="list-style-type: none"> ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment □ APPENDICES □ REGIONAL INFORMATION 				
BIOPHARMACEUTICS					
8.	<p>If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies:</p> <ul style="list-style-type: none"> • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided? 	<input type="checkbox"/>	<input type="checkbox"/>	X	
9.	<p>Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? <i>(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)</i></p>	X	<input type="checkbox"/>	<input type="checkbox"/>	Biopharm will verify it
10.	<p>Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.</p>	<input type="checkbox"/>	<input type="checkbox"/>	X	
11.	<p>For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?</p>	<input type="checkbox"/>	<input type="checkbox"/>	X	
12.	<p>For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?</p>	<input type="checkbox"/>	<input type="checkbox"/>	X	
13.	<p>Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?</p>	<input type="checkbox"/>	<input type="checkbox"/>	X	
REGIONAL INFORMATION AND APPENDICES					
14.	<p>Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?</p>	<input type="checkbox"/>	<input type="checkbox"/>	X	

C. FILING CONSIDERATIONS

15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	X	<input type="checkbox"/>	<input type="checkbox"/>	
16.	<p>Are the following information available in the Appendices for Biotech Products [3.2.A]?</p> <ul style="list-style-type: none"> <input type="checkbox"/> facilities and equipment <ul style="list-style-type: none"> <input type="checkbox"/> manufacturing flow; adjacent areas <input type="checkbox"/> other products in facility <input type="checkbox"/> equipment dedication, preparation, sterilization and storage <input type="checkbox"/> procedures and design features to prevent contamination and cross-contamination <input type="checkbox"/> adventitious agents safety evaluation (viral and non-viral) e.g.: <ul style="list-style-type: none"> <input type="checkbox"/> avoidance and control procedures <input type="checkbox"/> cell line qualification <input type="checkbox"/> other materials of biological origin <input type="checkbox"/> viral testing of unprocessed bulk <input type="checkbox"/> viral clearance studies <input type="checkbox"/> testing at appropriate stages of production <input type="checkbox"/> novel excipients 	<input type="checkbox"/>	<input type="checkbox"/>	X	
17.	<p>Are the following information available for Biotech Products:</p> <ul style="list-style-type: none"> <input type="checkbox"/> Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example: <ul style="list-style-type: none"> <input type="checkbox"/> LAL instead of rabbit pyrogen <input type="checkbox"/> Mycoplasma <p>Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples</p>				

1D: Product Design FMECA – Parenteral Drug Products

PRODUCT PROPERTY/IMPACT OF CHANGE/CQAS	CHANGES & VARIATIONS	FAILURE MODE	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	RPN
Sterility	<ul style="list-style-type: none"> • Formulation • Container closure • Process parameters • Scale/equipments • Site 	• Non-sterile unit(s)	4	IV (5)	5	100
Endotoxin Pyrogen	<ul style="list-style-type: none"> • Formulation • Container closure • Process parameters • Scale/equipments • Site 	• Excessive Endotoxin Levels	Others (2)	4	4	32
Assay (API), stability	<ul style="list-style-type: none"> • Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site 	(b) (4)	Highly stable drug (1)	2	1	2
Uniformity of Dose (Fill Volume/deliverable volume)	<ul style="list-style-type: none"> • Formulation • Container closure • Process parameters • Scale/equipments • Site 	• Insufficient dose	2	HRD (4)	2	16
Osmolality	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipments • Site 	<ul style="list-style-type: none"> • Irritation • Edema 	2	LVP (5)	2	20
pH- (Low)	<ul style="list-style-type: none"> • Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site 	• Irritation	2	2	1	4
Particle size distribution (suspension)	<ul style="list-style-type: none"> • Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site 	<ul style="list-style-type: none"> • Bioavailability • Embolism 	3	IV (5)	3	45
Particulate matter (non aggregate for solution only)	<ul style="list-style-type: none"> • Formulation • Container closure • Raw materials • Process parameters • Scale/equipments 	<ul style="list-style-type: none"> • Irritation • Embolism 	3	IV (5)	3	45

1D: Product Design FMECA – Parenteral Drug Products

PRODUCT PROPERTY/IMPACT OF CHANGE/CQAS	CHANGES & VARIATIONS	FAILURE MODE	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	RPN
	<ul style="list-style-type: none"> • Site 					
Leachable extractables	<ul style="list-style-type: none"> • Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site 	<ul style="list-style-type: none"> • Generation of impurities 	2	4	3	24
Appearance (Color/turbidity)	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipments • Site 	<ul style="list-style-type: none"> • Degradation 	3	3	1	9

Signed on behalf of Dr. Liang Zhou (Olen Stephens, Ph.D.)

Olen Stephens
-S

Digitally signed by Olen Stephens -S
 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Olen Stephens -S, 0.9.2342.19200300.100.1.1=2000558826
 Date: 2015.09.15 15:19:06 -04'00'



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg. 51, 10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 09/14/2015
To: Administrative File, STN 207793/0
From: Michael Shanks, Biologist, CDER/OPQ/OPF/DIA
Endorsement: Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA
Subject: Original NDA
US License: Pending
Applicant: MERRIMACK PHARMACEUTICALS INC
Mfg Facility: Drug Substance: (b) (4) (FEI (b) (4))
(b) (4) Drug Product: Merrimack Pharmaceuticals, Inc. (FEI 3008532848)
Drug Product (b) (4) (FEI (b) (4))
Product: Onivyde™ (irinotecan liposome injection)
Dosage: A 10 mL single-use vial containing 5 mg/mL of irinotecan hydrochloride trihydrate solution to deliver a dose of 50 mg.
Indication: For the treatment of pancreatic cancer.
Due Date: 10/24/2015

RECOMMENDATION: This submission is recommended for approval from a facility review perspective.

SUMMARY

The subject NDA proposes Drug Substance and Drug Product manufacture of Onivyde™ (irinotecan liposome injection) at the facilities described. Onivyde™ (irinotecan liposome injection) is manufactured as a 10 mL single-use vial containing 5 mg/mL of irinotecan hydrochloride trihydrate solution to deliver a dose of 50 mg via intravenous infusion is for the treatment of metastatic adenocarcinoma of the pancreas, in combination with 5- fluorouracil (5-FU) and leucovorin (LV), in patients previously treated with gemcitabine. Detailed drug substance manufacturing information is included in Drug Master File DMF (b) (4) Drug Product manufacturing is described in NDA 207793 Module 2.3.P.3.

ASSESSMENT

Best Available Copy

INITIAL FACILITY RISK ASSESSMENT

Initial Facility Risk Assessment

ANDA 207793
PDUFA 10/24/16

OPF Reviewer Michael Shanks
Date 6/6/2016

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment	Recommendation
(b) (4)	(b) (4)	CTL	Deburden testing, Particulate testing, Stability testing, Raw material testing	15	5	0	20	Approve on Profile 10/24/2015
		CTL	Raw material testing, Drug Substance testing	43	5	0	48	Approve on DO recommendation 10/24/2015
		CTL	Endotoxin Testing	5	5	0	10	Approve on Profile 10/24/2015
		CSW	Manufacture of the drug substance	9	6	0	15	Approve on Profile 10/24/2015
		CTL	Container closure integrity testing	1	5	0	6	Approve on DO recommendation 10/24/2015
		CTL	Raw material testing, Drug Substance testing	9	5	0	14	Approve on Profile 10/24/2015
		SVS	Labeling, Packaging	5	15	0	20	Approve on Profile 10/24/2015
		SVS	Drug product manufacture	40	15	6	55	Approve on DO recommendation 10/24/2015
Merrimack Pharmaceuticals, Inc.	30145328-08	(b) (4)		30	36	0	66	NE District Inspection and Review Recommendation Approved

DRUG SUBSTANCE FACILITIES

3.2. Manufacturers:

The sites proposed for Onivyde™ (irinotecan liposome injection) DS and DP manufacture, and testing are presented below in Table 1.

TABLE 1. Proposed Sites for Onivyde™ (irinotecan liposome injection) DS and DP manufacture, and testing.

Establishment name	FEI Number	Responsibilities and profile codes	Initial Risks Identified	Current Status	Final Recommendation
	(b) (4)	CTL – Bioburden testing, Particulate testing, Sterility testing, Raw material testing	Low	Last inspection for profile code (b) (4) with a status of VAI.	Acceptable based on history/profile, approved based on profile
Merrimack Pharmaceuticals, Inc.	3008532848	(b) (4)	New facility with no inspectional history	The GMP and Pre-approval inspection was conducted and the NE District recommended PAI approval.	Acceptable based on District PAI and File Review
	(b) (4)	CTL – Raw material testing, Drug Substance testing	Previous two inspections were OAI downgraded to VAI. Requested District Office Recommendation.	Last inspection (b) (4) downgraded status of VAI. Prior inspection (b) (4) for profile code CTL with a downgraded status of VAI.	Acceptable based on District File Review.
		CTL – Endotoxin Testing	Low	The last inspection on (b) (4) was VAI for the profile CTL.	Acceptable based on history/profile, approved based on profile.
		CSN - Manufacture of the drug substance	Low	Last inspection (b) (4) for profile code CSN with a status of VAI.	Acceptable based on history/profile, approved based on profile.
		CTL - Container closure integrity testing	Low	Last inspection (b) (4) for profile code CTL with a status of NAI.	Acceptable based on history/profile and District t approval recommendation.
		CTL - Raw material testing, Drug Substance testing.	Low	The last inspection on (b) (4) was VAI for the profile CTL.	Acceptable based on history/profile, approved based on profile.
		SVS - Labeling, Packaging	Low	The last inspection on (b) (4) was VAI for the profile SVS.	Acceptable based on history/profile, approved based on profile
		SVS - Drug product manufacture.	Low	The last inspection on (b) (4) was VAI for the profile SVS.	Acceptable based on District File Review

Facility Overview Summary:



(b) (4) is acceptable for irinotecan liposome injection container closure integrity testing.

Reviewer Comment: *The compliance status of the facilities for the manufacture of Onivyde™ (irinotecan liposome injection) DS and DP, labeling and packaging, and testing are acceptable.*

CONCLUSION

Adequate descriptions were provided for the (b) (4). (FEI (b) (4)), Merrimack Pharmaceuticals, Inc. (FEI 3008532848), and (b) (4). (FEI (b) (4)) facilities proposed for Onivyde™ (irinotecan liposome injection) DS and DP manufacture. All proposed manufacturing, labeling and packaging, and testing sites are recommended for approval from a facilities assessment standpoint.

Michael R.
Shanks -S

Digitally signed by Michael R. Shanks -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=2001408917,
cn=Michael R. Shanks -S
Date: 2015.09.11 16:47:26 -04'00'

Michael Shanks
Biologist
OPF Division of Inspectional Assessment
Branch 1

Zhihao Qiu -
S

Digitally signed by Zhihao Qiu -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Zhihao Qiu -S,
0.9.2342.19200300.100.1.1=2000438274
Date: 2015.09.14 08:01:02 -04'00'

Zhihao Peter Qiu, Ph.D.
Branch Chief
OPF Division of Inspectional Assessment
Branch 1

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY GRACE LUBAO
11/04/2015