

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**202497Orig1s000**

**CHEMISTRY REVIEW(S)**

# Memorandum

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**To:** NDA 202-497  
**Through:** Janice Brown, M.S.  
**From:** Xiao Hong Chen, Ph.D.  
**Date:** 8/3/2012  
**Re:** Final Recommendation for the NDA 202-497

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CMC information for NDA 202-497 have been reviewed and found to be acceptable. Refer to the CMC review #1 and #2 dated 13-APR-2012 and 14-JUN-2012, respectively, in Dartrts.

On August 2, 2012, Office of Compliance issued an overall “Acceptable” recommendation for NDA 202-497 through EES. Also note that all the deficiencies in the microbiology have been satisfactorily resolved and Dr. Vinayak Pawar has recommended “Approval” in his review dated 25-JUL-2012.

The container carton labeling is under final revisions by DMEPA.

This NDA is recommended for approval from the CMV standpoint.

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

XIAO H CHEN  
08/03/2012

JANICE T BROWN  
08/06/2012  
Janice Brown for Nallaperum Chidambaram  
Recommend AP from a CMC standpoint

**NDA 202-497**

**Marqibo® (vinCRISTine sulfate LIPOSOME injection)  
(5 mg/31 mL)**

**Talon Therapeutics Incorporated**

**Xiao-Hong Chen, Ph.D.**

**Office of New Drug Quality Assessment  
Division of New Drug Quality Assessment I**

**CMC Review of NDA 202-497**

**For the Division of Hematology Products (HFD-160)**

# Table of Contents

<b>Table of Contents</b> .....	<b>2</b>
<b>Chemistry Review Data Sheet</b> .....	<b>3</b>
<b>West Pharmaceuti-cal Services</b> .....	<b>5</b>
<b>The Executive Summary</b> .....	<b>8</b>
<b>I. Recommendations</b> .....	<b>8</b>
<b>A. Recommendation and Conclusion on Approvability</b> .....	<b>8</b>
<b>B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.</b> .....	<b>8</b>
<b>II. Summary of Chemistry Assessments</b> .....	<b>8</b>
<b>A. Description of the Drug Product(s) and Drug Substance(s)</b> .....	<b>8</b>
<b>B. Description of How the Drug Product is Intended to be Used</b> .....	<b>10</b>
<b>C. Basis for Approvability Recommendation</b> .....	<b>10</b>
<b>III. Administrative</b> .....	<b>11</b>
A. Reviewer's Signature.....	11
<b>See appended electronic signature page.</b> .....	<b>11</b>
B. Endorsement Block.....	11
C. CC Block.....	11
<b><u>Chemistry Assessment</u></b> .....	<b>12</b>
<b>III. List Of Deficiencies/Comments To Be Communicated</b> .....	<b>21</b>

# Chemistry Review Data Sheet

1. NDA 202-497
2. REVIEW #2
3. REVIEW DATE: 14-JUN-2012
4. REVIEWER: Xiao-Hong Chen, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

Original NDA submission  
Amendment SN0009  
Amendment SN0012

Document Date

July 13, 2011  
February 13, 2012  
April 10, 2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Amendment SN0014  
Amendment SN0013  
Amendment SN0012

Document Date

April 19, 2012  
April 12, 2012  
April 10, 2012

7. NAME & ADDRESS OF APPLICANT:

Name: Talon Therapeutics Incorporated  
Address: 2207 Bridgepointe Parkway, Suite 250  
San Mateo, CA 94404

N202-497 Review #2

4

Representative: Thomas J Tarlow, VP, Regulatory Affairs and  
Quality Assurance

Telephone: (650)588-2787

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Marqibo®
- b) Non-Proprietary Name (USAN): vincristine sulfate liposome injection
- c) Code Name/# N/A
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 3
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: Filed 505(b)(2)

10. PHARMACOL. CATEGORY: Philadelphia chromosome negative acute lymphoblastic leukemia (ALL) in second relapse

11. DOSAGE FORM: Liposome Injection (kit presentation)

12. STRENGTH/POTENCY: 5 mg/31 mL

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED:  Rx  OTC

15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):**

SPOTS product – Form Completed

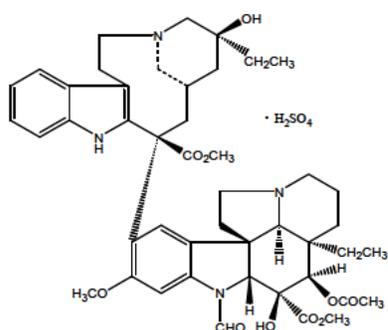
Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

## Executive Summary Section

N202-497 Review #2

5



Name	Vincristine (INN) Vincristine Sulphate (Ph Eur, BAN) Vincristine Sulfate (JAN)
Chemical Name	22-Oxovincaleukoblastine sulfate salt (1:1) Leurocristine sulfate salt (1:1)
CAS number	2068-78-2
Molecular Weight	923.04 (Salt form)
Molecular Formula	$C_{46}H_{56}N_4O_{10} \cdot H_2SO_4$
Structural formula	See above

## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENT
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	2-9-2012	Reviewed by Debasis Ghosh
	III			3	Adequate	12-14-2004	None
	III			3	Adequate	12-9-2011	Reviewed by Yarery C Smith
	III			4	N/A	3-15-2012	None
	III			3	Adequate	9-15-2003	None
	III			3	Adequate	4-10-2010	Reviewed by Joel S. Hathaway
	III			3	Adequate	3-9-2004	None

Executive Summary Section

N202-497 Review #2

6

(b) (4)	IV	(b) (4)	1	Adequate	2-3-2012	Reviewed by Debasis Ghosh
	IV		1	Adequate	2-3-2012	Reviewed by Debasis Ghosh
	IV		3	Adequate	12-13-2011	Reviewed by Yarery C Smith

<sup>1</sup> Action codes for DMF Table:

- 1 – DMF Reviewed.
- Other codes indicate why the DMF was not reviewed, as follows:
- 2 –Type 1 DMF
- 3 – Reviewed previously and no revision since last review
- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Supporting Documents:**

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

**C. Related Documents:**

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	59,056	INEX Pharmaceuticals	Original IND submitted on 01-Oct-1999.
NDA	21600	INEX Pharmaceuticals	Original 505(b)(2) NDA (Type 3) submitted on 15-Mar-2004 to seek approval for the treatment of patients with aggressive Non-Hodgkin's Lymphoma previously treated with at least two combination chemotherapy regimens. A not approvable letter was issued to INEX due to clinical and CMC deficiencies.

18. CONSULTS/CMC-RELATED REVIEWS:

## Executive Summary Section

N202-497 Review #2

7

CONSULTS	RECOMMENDATION	DATE	REVIEWER
EES	Pending	14-JUN-2012	Office of Compliance
Biopharmaceutics	Acceptable	11-APR-2012	John Duan
Proprietary Name	Acceptable	15-DEC-2011	Jibril Abdus-Samad, PharmD
Methods Validation	Acceptable	05-MAR-2012	DPA has evaluated the IVR method requested by the Biopharm reviewer Dr. Duan, and found it acceptable. However, comments have been generated to be conveyed to Talon.
EA (Categorical exclusion)	Acceptable	30-APR-2012	Xiao Hong Chen
Microbiology	Pending	5-APR-2012	Vinayak Pawar

# The Chemistry Review for NDA 202-497

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From a CMC perspective, this application is recommended for approval provided that an overall “Acceptable” EES recommendation and an “Acceptable” recommendation from microbiology review are provided. All CMC review deficiencies/comments have been satisfactorily addressed. The container carton labeling and the proposed Package Insert are still under review and revision.

Also note that the Microbiology review is still pending, an overall recommendation regarding approvability has not been issued from a Microbiology standpoint, and final labeling is still pending.

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

N/A.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### **Drug Product**

Marqibo® is indicated for the treatment of adult patients with Philadelphia Chromosome negative (Ph-) acute lymphoblastic leukemia (ALL) in second or greater relapse or whose disease has progressed following two or more treatment lines of anti-leukemia therapy. Marqibo (vinCRISTine sulfate LIPOSOME injection) (5 mg/31 mL) (VSLI) is supplied as a 3-vial kit for constitution to prepare liposome encapsulated vincristine at the pharmacy. Prior to administration, the kit's components are mixed in a prescribed manner to load the active ingredient, vincristine, into the sphingomyelin/cholesterol (SM/Chol) liposome. Following constitution, VSLI is a white to off-white, homogenous, translucent suspension, which is diluted with standard diluents (5% Dextrose or 0.9% Sodium Chloride) prior to IV infusion.

Manufacturing of Marqibo consists of the production of each individual component as listed below and packaging of all the components into the kit:

- Vincristine Sulfate Injection USP (5 mg/ 5 mL) (VSI)
- Sphingomyelin/Cholesterol Liposome Injection (103 mg/mL) (SCLI)

## Executive Summary Section

N202-497 Review #2

9

- Sodium Phosphate Injection (355 mg/25 mL) (SPI)

Manufacturing of VSI is the same as that of the RLD, Vincristine Sulfate Injection, USP. Manufacturing of SPI and SCLI were developed by INEX, the sponsor of the initial IND 59,056 and previous NDA 21-600. In support of Phase I and Phase II clinical trials for VSLI, (b) (4) have been used to manufacture the SCLI liposome. The (b) (4) was used to manufacture the liposome used to formulate VSLI for Phase I and IIa clinical trials. The (b) (4) was later developed to facilitate the anticipated scale-up of the commercial production. The SCLI liposome manufactured using the (b) (4) was used in the pivotal Phase II clinical trial.

During the initial drug development, (b) (4) was later replaced by the 3-vial kit format without changing formulation of any of the kit components to simplify the constitution procedures. The 3-vial kit presentation has been used in all the pivotal clinical trials to support the approval of the indication sought. INEX has conducted technical compatibility studies to demonstrate that the (b) (4) and the 3-vial kit are comparable.

The specifications are proposed for individual components of the kit as well as for the constituted VSLI product. Specifications for VSI are based on USP compendial monograph. Specifications for SCLI have been revised by the applicant (i.e. particle size distribution and (b) (4) in response to the FDA's comments. The revised specifications for SCLI would ensure improved quality control and performance of SCLI liposome. Specifications for VSLI (especially particle size mean and distribution) are also revised in response to the FDA comments. In vitro drug release specification of VSLI was evaluated by the biopharmaceutics reviewer, Dr. John Duan, and the proposed revised specification is found to be acceptable. The biopharmaceutics review recommended "acceptable" for this application.

Stability studies for VSLI drug product include stability testing for each individual component and the constituted VSLI. The shelf life of VSLI is determined in such a way that shortest expiry of all three components will be the expiration date for VSLI. A 24-month shelf life for the Marqibo VSLI kit stored at 5°C protected from light (VSLI is light sensitive) was proposed and is found to be acceptable based on the stability data generated for each individual component of the kit and those of VSLI. An in-use stability study was conducted that demonstrated the diluted drug is physico-chemically stable for 12 hours when stored at 5 to 25°C in the dark or in typical room light. The microbiology stability of the diluted drug is evaluated by the microbiology reviewer, Dr. Vinayak Pawar. Based on Dr. Pawar's assessment, the in-use stability study is acceptable from the microbiology perspective. The microbiology review for the NDA is still pending. **Based on the stability data provided, the proposed expiry of 24 months stored at 2-8°C (36-46°F) can be granted.**

Robustness studies were conducted to assess the impact of various constitution procedures such as temperature, incubation time, order of addition, and other parameters that would affect on the loading and stability of the VSLI drug product. The results demonstrated that the constitution

## Executive Summary Section

N202-497 Review #2

10

procedure was fairly robust in terms of mixing sequence, temperature ( $65 \pm 5^\circ\text{C}$ ), time with a defined range of parameters. A human factor study was conducted to show that the 20 pharmacists, who were not previously trained in the constitution process, would be able to properly prepare VSLI by following the constitution instructions in the PI, and the VSLI final product conformed to the specifications. However, concerns regarding the design of the study (without including two end user groups in the study: pharmacy technicians and oncology nurses) have been raised by DMEPA, and Talon was asked to design and conduct the human factor study to include these two groups (refer to Amy Baird's email communication to Talon dated 05-Apr-2012). In addition, there is a sterility concern due to the multiple manipulations during constitution procedures. This issue is evaluated by the microbiology reviewer of the NDA. Refer to the reviews from DMEPA and Microbiology.

CMC information for the novel excipient, sphingomyelin, is provided in DMF (b) (4). The DMF was reviewed by Dr. Debasis Ghosh, and was found to be adequate to support the NDA.

### **Drug Substance**

The drug substance, vincristine sulfate, is an indole alkaloid compound derived from *Vinca rosea* (*Catharanthus roseus*) leaves. It is a white to slightly yellowish crystalline powder. It is freely soluble in water, soluble in methanol and slightly soluble in alcohol. It has a molecular weight of 923.0 (salt form). Vincristine sulfate is the active ingredient in several FDA approved drugs such as Eli Lilly Pharmaceuticals' Oncovin® (NDA 014103) and Hospira's Vincristine Sulfate Injection USP, 1 mg/1 mL and 2 mg/2 mL, (ANDA 71-484 and ANDA 71-559, respectively). It is also a subject of the British Pharmacopoeia (BP), European Pharmacopoeia (Ph. Eur.) and United States Pharmacopeia (USP). Vincristine sulfate is manufactured by (b) (4). Complete manufacturing information for vincristine sulfate is provided in Type II DMF 4561. The supplier for vincristine sulfate for this NDA is Fine Chemicals Corporation located in South Africa, (b) (4). Vincristine sulfate manufactured by Fine Chemicals meets the USP monograph requirements. Review for DMF 4561 has been completed by Dr. Ghosh and the DMF is found to be adequate.

### **B. Description of How the Drug Product is Intended to be Used**

Marqibo® is to be administered by intravenous infusion for 1 hour at a dose of  $2.25 \text{ mg/m}^2$  weekly. Prior to administration, the 3 components of the kit (VSI, SCLI and SPI) must be mixed to prepare VSLI (5 mg/31 mL) following the procedures in the Package Insert, and diluted with a diluent in the I.V. bag containing either 5% dextrose injection or 0.9% sodium chloride injection.

### **C. Basis for Approvability Recommendation**

All CMC review deficiencies/comments have been satisfactorily resolved. An overall EES recommendation and microbiology review are still pending. The NDA is recommended for approval from the CMC review perspective, pending an "Acceptable" recommendation from EES and an approval recommendation from microbiology.

Executive Summary Section

N202-497 Review #2

11

**III. Administrative**

A. Reviewer's Signature

**See appended electronic signature page.**

B. Endorsement Block

Reviewer Name/Date: Xiao-Hong Chen, Ph.D.

Branch Chief Name/Date: Sarah Pope Miksinski, Ph.D.

C. CC Block

Amy Baird/OODP/DHP/Regulatory PM

Janice Brown/ONDQA/CMC Lead

Jewell Martin/ONDQA/PM

Sarah Pope Miksinski/ONDQA/Branch Chief

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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XIAO H CHEN  
06/15/2012

JANICE T BROWN  
06/15/2012

**NDA 202-497**

**Marqibo® (vincristine sulfate liposome injection)  
(5 mg/31 mL)**

**Talon Therapeutics Incorporated**

**Xiao-Hong Chen, Ph.D.**

**Office of New Drug Quality Assessment  
Division of New Drug Quality Assessment I**

**CMC Review of NDA 202-497**

**For the Division of Hematology Products (HFD-160)**

# Table of Contents

<b>Table of Contents .....</b>	<b>2</b>
<b>Chemistry Review Data Sheet.....</b>	<b>4</b>
<b>The Executive Summary .....</b>	<b>9</b>
<b>I. Recommendations .....</b>	<b>9</b>
A. Recommendation and Conclusion on Approvability .....	9
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	10
<b>II. Summary of Chemistry Assessments .....</b>	<b>10</b>
A. Description of the Drug Product(s) and Drug Substance(s) .....	10
B. Description of How the Drug Product is Intended to be Used.....	12
C. Basis for Approvability Recommendation.....	12
<b>III. Administrative .....</b>	<b>12</b>
A. Reviewer's Signature.....	12
See appended electronic signature page.....	12
B. Endorsement Block.....	12
C. CC Block.....	12
<b>Chemistry Assessment .....</b>	<b>14</b>
<b>I. Review Of Common Technical Document-Quality (CTD-Q) Module 3.2 .....</b>	<b>14</b>
<b>S DRUG SUBSTANCE [Vincristine Sulfate, Fine Chemicals Corp] .....</b>	<b>14</b>
S.1 General Information [Vincristine Sulfate, Fine Chemicals Corp] .....	14
S.2 Manufacture [Vincristine Sulfate, Fine Chemicals Corp] .....	16
S.3 Characterization [Vincristine Sulfate, Fine Chemicals Corp] .....	17
S.4 Control of Drug Substance [Vincristine Sulfate, Fine Chemicals Corp].....	18
S.5 Reference Standards or Materials [Vincristine Sulfate, USP] .....	21
S.6 Container Closure System.....	21
S.7 Stability [Vincristine Sulfate, Fine Chemicals Corp] .....	21
<b>P DRUG PRODUCT [vincristine sulfate injection (VSI)] .....</b>	<b>22</b>
P.1 Description and Composition of the Drug Product [VSI] .....	23
P.2 Pharmaceutical Development [VSI] .....	24

P.3	Manufacture [VSI] .....	28
P.4	Control of Excipients [VSI] .....	32
P.5	Control of Drug Product [VSI] .....	34
P.6	Reference Standards or Materials [VSI] .....	38
P.7	Container Closure System [VSI] .....	38
P.8	Stability [VSI] .....	40
P	DRUG PRODUCT [Sphingomyelin/Cholesterol Liposome Injection (SCLI)] .....	45
P.1	Description and Composition of the Drug Product [SCLI] .....	45
P.2	Pharmaceutical Development [SCLI] .....	46
P.3	Manufacturer [SCLI] .....	46
P.4	<i>Control of Excipients [SCLI]</i> .....	66
P.5	Control of Drug Product [SCLI] .....	71
P.6	Reference Standards or Materials [SCLI] .....	84
P.7	Container Closure System [SCLI] .....	84
P.8	Stability [SCLI] .....	86
P	DRUG PRODUCT [Sodium Phosphate Injection (SPI)] .....	89
P.1	Description and Composition of the Drug Product [SPI] .....	89
P.2	Pharmaceutical Development [SPI] .....	90
P.3	Manufacture [SPI] .....	92
P.4	Control of Excipients [SPI] .....	97
P.5	Control of Drug Product [SPI] .....	97
P.6	Reference Standards or Materials [SPI] .....	101
P.7	Container Closure System [SPI] .....	101
P.8	Stability [SPI] .....	102
P	DRUG PRODUCT [Vincristine Sulfate Liposome Injection (VSLD)] .....	105
P.1	Description and Composition of the Drug Product [VSLI] .....	105
P.2	Pharmaceutical Development [VSLI] .....	108
P.3	Manufacture [VSLI] .....	124
P.4	Control of Excipients [VSLI] .....	130
P.5	Control of Drug Product [VSLI] .....	132
P.6	Reference Standards or Materials [VSLI] .....	142
P.7	Container Closure System [VSLI] .....	142
P.8	Stability [VSLI] .....	142
A	APPENDICES .....	147
R	REGIONAL INFORMATION .....	147
II.	Review Of Common Technical Document-Quality (CTD-Q) Module 1 .....	148
A.	Labeling & Package Insert .....	148
B.	Environmental Assessment Or Claim Of Categorical Exclusion .....	153
III.	List Of Deficiencies/Comments To Be Communicated .....	153

# Chemistry Review Data Sheet

1. NDA 202-497
2. REVIEW #1:
3. REVIEW DATE: 13-APR-2012
4. REVIEWER: Xiao-Hong Chen, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

Previous NDA 21600 submission  
Amendment  
Amendment  
Amendment

Document Date

March 12, 2004  
July 14, 2004  
September 30, 2004  
December 3, 2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original NDA submission  
Amendment SN0009  
Amendment SN0012

Document Date

July 13, 2011  
February 13, 2012  
April 10, 2012

7. NAME & ADDRESS OF APPLICANT:

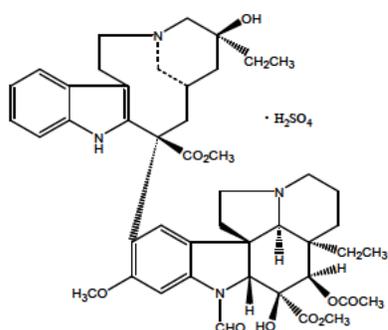
Name: Talon Therapeutics Incorporated  
Address: 2207 Bridgepointe Parkway, Suite 250  
San Mateo, CA 94404



## Executive Summary Section

N202-497 Review #1

6



Name	Vincristine (INN) Vincristine Sulphate (Ph Eur, BAN) Vincristine Sulfate (JAN)
Chemical Name	22-Oxovincal leukoblastine sulfate salt (1:1) Leurocristine sulfate salt (1:1)
CAS number	2068-78-2
Molecular Weight	923.04 (Salt form)
Molecular Formula	$C_{46}H_{56}N_4O_{10} \cdot H_2SO_4$
Structural formula	See above

## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENT
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	2-9-2012	Reviewed by Debasis Ghosh
	III			3	Adequate	12-14-2004	None
	III			3	Adequate	12-9-2011	Reviewed by Yarery C Smith
	III			4	N/A	3-15-2012	None
	III			3	Adequate	9-15-2003	None
	III			3	Adequate	4-10-2010	Reviewed by Joel S. Hathaway
	III			3	Adequate	3-9-2004	None

Executive Summary Section

N202-497 Review #1

7

		cal Services					
(b) (4)	IV		(b) (4)	1	Adequate	2-3-2012	Reviewed by Debasis Ghosh
	IV			1	Adequate	2-3-2012	Reviewed by Debasis Ghosh
	IV			3	Adequate	12-13-2011	Reviewed by Yarery C Smith

<sup>1</sup> Action codes for DMF Table:

- 1 – DMF Reviewed.
- Other codes indicate why the DMF was not reviewed, as follows:
- 2 –Type 1 DMF
- 3 – Reviewed previously and no revision since last review
- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Supporting Documents:**

Doc #	OWNER	ITEM REFERENCED	STATU S	DATE REVIEW COMPLETED	COMMENTS

**C. Related Documents:**

DOCUMENT	APPLICATI ON NUMBER	OWNER	DESCRIPTION/COMMENT
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NDA	21600	INEX Pharmaceuticals	Original 505(b)(2) NDA (Type 3) submitted on 15-Mar-2004 to seek approval for the treatment of patients with aggressive Non-Hodgkin’s Lymphoma previously treated with at least two combination chemotherapy regimens. A not approvable letter was issued to INEX due to clinical and CMC deficiencies.

18. CONSULTS/CMC-RELATED REVIEWS:

## Executive Summary Section

N202-497 Review #1

8

CONSULTS	RECOMMENDATION	DATE	REVIEWER
EES	Pending	10-APR-2012	Office of Compliance
Biopharmaceutics	Acceptable	11-APR-2012	John Duan
Proprietary Name	Acceptable	15-DEC-2011	Jibril Abdus-Samad, PharmD
Methods Validation	Acceptable	05-MAR-2012	DPA has evaluated the IVR method requested by the Biopharm reviewer Dr. Duan, and found it acceptable. However, comments have been generated to be conveyed to Talon.
EA (Categorical exclusion)	Not acceptable	10-APR-2012	Xiao Hong Chen
Microbiology	Pending	5-APR-2012	Vinayak Pawar

# The Chemistry Review for NDA 202-497

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From a CMC perspective, this application is recommended for a **Complete Response** action. The following issues need to be completely resolved before this NDA can be recommended for approval. 1) An overall acceptable recommendation from the Office of Compliance; 2) Satisfactorily resolving the CMC deficiencies listed as follows;

1. The requested VSI impurity profile comparison between your VSI lots and RLD was not provided in the Amendment (SN0009) dated February 13, 2012. Provide full comparative data for the complete impurity profiles of the proposed VSI formulation (at least 3 lots) and the reference listed drug, i.e. list all individual related substances with their RRTs (relative retention time).
2. Regarding the VSI OOS results at the accelerated conditions at 3 and 6 months, although you provided up to 2 months stability data (one month data for 3 lots and two months data for 1 lot) at the accelerated conditions of 25°C/60% RH in the amendment, you did not provide the shipping conditions, such as duration and temperature. Therefore, you did not adequately address the concern regarding two months stability data at 25°C/60% RH being sufficient to support the shipping and handling conditions for both VSI and VSLI.
3. Include the proposed acceptance limit for unspecified degradation products of no more than [REDACTED] <sup>(b) (4)</sup> in the table for SCLI specification.
4. You have stated that vincristine sulfate is a natural product that is one of the over 70-member vinca alkaloid chemical family isolated from the periwinkle plant *Catharanthus roseus* (Madagascar periwinkle). Provide the source of the raw material, the periwinkle plant, and indicate whether it is grown as a wild plant or cultivated plant. If it is a wild grown plant, you will need to file an Environmental Assessment (EA). If it is cultivated non-wild grown plant, you may claim categorical exclusion under 21 CFR 25.31(a) and/or 21 CFR 25.31 (c). Please refer to the attached FDA document regarding EA Review Requirements for Drugs Derived from Plant Sources.

Also note that the Microbiology review is still pending, an overall recommendation regarding approvability has not been issued from a Microbiology standpoint, and final labeling is still pending.

## Executive Summary Section

N202-497 Review #1

10

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

N/A.

**II. Summary of Chemistry Assessments****A. Description of the Drug Product(s) and Drug Substance(s)****Drug Product**

Marqibo® is indicated for the treatment of adult patients with Philadelphia Chromosome negative (Ph-) acute lymphoblastic leukemia (ALL) in second or greater relapse or whose disease has progressed following two or more treatment lines of anti-leukemia therapy. Marqibo (vincristine sulfate liposome injection) (5 mg/31 mL) (VSLI) is supplied as a 3-vial kit for constitution to prepare liposome encapsulated vincristine at the pharmacy. Prior to administration, the kit's components are mixed in a prescribed manner to load the active ingredient, vincristine, into the sphingomyelin/cholesterol (SM/Chol) liposome. Following constitution, VSLI is a white to off-white, homogenous, translucent suspension, which is diluted with standard diluents (5% Dextrose or 0.9% Sodium Chloride) prior to IV infusion.

Manufacturing of Marqibo consists of the production of each individual component as listed below and packaging of all the components into the kit:

- Vincristine Sulfate Injection USP (5 mg/ 5 mL) (VSI)
- Sphingomyelin/Cholesterol Liposome Injection (103 mg/mL) (SCLI)
- Sodium Phosphate Injection (355 mg/25 mL) (SPI)

Manufacturing of VSI is the same as that of the RLD, Vincristine Sulfate Injection, USP.

Manufacturing of SPI and SCLI were developed by INEX, the sponsor of the initial IND 59,056 and previous NDA 21-600. In support of Phase I and Phase II clinical trials for VSLI, (b) (4) have been used to manufacture the SCLI liposome. The (b) (4) was used to manufacture the liposome used to formulate VSLI for Phase I and IIa clinical trials. The (b) (4) was later developed to facilitate the anticipated scale-up of the commercial production. The SCLI liposome manufactured using the (b) (4) were used in the pivotal Phase II clinical trial.

During the initial drug development, (b) (4) was later replaced by the 3-vial kit format without changing formulation of any of the kit components to simplify the constitution procedures. The 3-vial kit presentation has been used in all the pivotal clinical trials to support the approval of the indication sought. INEX has conducted technical compatibility studies to demonstrate that the (b) (4) and the 3-vial kit are comparable.

## Executive Summary Section

N202-497 Review #1

11

The specifications are proposed for individual components of the kit as well as for the constituted VSLI product. Specifications for VSI are based on USP compendial monograph. Specifications for SCLI have been revised by the applicant (i.e. particle size distribution and (b) (4)) in response to the FDA's comments. The revised specifications for SCLI would ensure improved quality control and performance of SCLI liposome. Specifications for VSLI (especially particle size mean and distribution) are also revised in response to the FDA comments. In vitro drug release specification of VSLI was evaluated by the biopharmaceutics reviewer, Dr. John Duan, and the proposed revised specification is found to be acceptable. The biopharmaceutics review recommended "acceptable" for this application.

Stability studies for VSLI drug product include stability testing for each individual component and the constituted VSLI. The shelf life of VSLI is determined in such a way that shortest expiry of all three components will be the expiration date for VSLI. A 24-month shelf life for the Marqibo VSLI kit stored at 5°C protected from light (VSLI is light sensitive) was proposed and is found to be acceptable based on the stability data generated for each individual component of the kit and those of VSLI. An in-use stability study was conducted that demonstrated the diluted drug is physico-chemically stable for 12 hours when stored at 5 to 25°C in the dark or in typical room light. The microbiology stability of the diluted drug is evaluated by the microbiology reviewer, Dr. Vinayak Pawar. Based on Dr. Pawar's assessment, the in-use stability study is acceptable from the microbiology perspective. The microbiology review for the NDA is still pending. Based on the stability data provided, the proposed expiry of 24 months stored at 2-8°C (36-46°F) can be granted.

Robustness studies were conducted to assess the impact of various constitution procedures such as temperature, incubation time, order of addition, and other parameters that would affect on the loading and stability of the VSLI drug product. The results demonstrated that the constitution procedure was fairly robust in terms of mixing sequence, temperature ( $65 \pm 5^\circ\text{C}$ ), time with a defined range of parameters. A human factor study was conducted to show that the 20 pharmacists, who were not previously trained in the constitution process, would be able to properly prepare VSLI by following the constitution instructions in the PI, and the VSLI final product conformed to the specifications. However, concerns regarding the design of the study (without including two end user groups in the study: pharmacy technicians and oncology nurses) have been raised by DMEPA, and Talon was asked to design and conduct the human factor study to include these two groups (refer to Amy Baird's email communication to Talon dated 05-Apr-2012). In addition, there is a sterility concern due to the multiple manipulations during constitution procedures. This issue is evaluated by the microbiology reviewer of the NDA. Refer to the reviews from DMEPA and Microbiology.

CMC information for the novel excipient, sphingomyelin, is provided in DMF (b) (4). The DMF was reviewed by Dr. Debasis Ghosh, and was found to be adequate to support the NDA.

**Drug Substance**

The drug substance, vincristine sulfate, is an indole alkaloid compound derived from *Vinca rosea* (*Catharanthus roseus*) leaves. It is a white to slightly yellowish crystalline powder. It is freely

## Executive Summary Section

N202-497 Review #1

12

soluble in water, soluble in methanol and slightly soluble in alcohol. It has a molecular weight of 923.0 (salt form). Vincristine sulfate is the active ingredient in several FDA approved drugs such as Eli Lilly Pharmaceuticals' Oncovin® (NDA 014103) and Hospira's Vincristine Sulfate Injection USP, 1 mg/1 mL and 2 mg/2 mL, (ANDA 71-484 and ANDA 71-559, respectively). It is also a subject of the British Pharmacopoeia (BP), European Pharmacopoeia (Ph. Eur.) and United States Pharmacopoeia (USP). Vincristine sulfate is manufactured (b) (4)

(b) (4) Complete manufacturing information for vincristine sulfate is provided in Type II DMF 4561. The supplier for vincristine sulfate for this NDA is Fine Chemicals Corporation located in South Africa, (b) (4)

(b) (4) Vincristine sulfate manufactured by Fine Chemicals meets the USP monograph requirements. Review for DMF 4561 has been completed by Dr. Ghosh and the DMF is found to be adequate.

### B. Description of How the Drug Product is Intended to be Used

Marqibo® is to be administered by intravenous infusion for 1 hour at a dose of 2.25 mg/m<sup>2</sup> weekly. Prior to administration, the 3 components of the kit (VSI, SCLI and SPI) must be mixed to prepare VSLI (5 mg/31 mL) following the procedures in the Package Insert, and diluted with a diluent in the I.V. bag containing either 5% dextrose injection or 0.9% sodium chloride injection.

### C. Basis for Approvability Recommendation

A "Complete Response" action is recommended for the NDA based on the following: 1) The overall recommendation from the Office of Compliance for pre-approval inspections is still pending; 2) Unresolved CMC deficiencies (see above); 3) Pending the microbiology review of the NDA.

## III. Administrative

### A. Reviewer's Signature

See appended electronic signature page.

### B. Endorsement Block

Reviewer Name/Date: Xiao-Hong Chen, Ph.D.

Branch Chief Name/Date: Sarah Pope Miksinski, Ph.D.

### C. CC Block

Amy Baird/OODP/DHP/Regulatory PM

Janice Brown/ONDQA/CMC Lead

Jewell Martin/ONDQA/PM

Sarah Pope Miksinski/ONDQA/Branch Chief

Executive Summary Section

N202-497 Review #1

13

Richard Lostritto/ONDQA/DNQA I Director

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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XIAO H CHEN  
04/13/2012

SARAH P MIKSINSKI  
04/13/2012

**Initial Quality Assessment  
Division of New Drug Quality Assessment I  
Branch II**

**OND Division:** Division of Hematology Products  
**NDA:** 202497  
**Applicant:** Talon Therapeutics, Inc.  
**Stamp Date:** 12-Jul-2011  
**PDUFA Date:** Priority 12-Jan-2012  
**Proprietary (Brand) Name of Drug Product:** Marqibo  
**Established Name:** Vincristine Sulfate Liposomes Injection  
**Dosage Form(s):** Injection (solution)  
**Strength(s):** Vincristine Sulfate Liposomes Injection (0.16 mg/mL)  
Kit components  
 Vincristine sulfate, USP (5 mg/5 mL)  
 Sphingomyelin/cholesterol liposomes injection (103 mg/mL, 1 mL)  
 Sodium phosphate injection (14.2 mg/mL, 25 mL)  
**Route of Administration:** Intravenous  
**Proposed Indication(s):** Treatment of adult patients with Philadelphia Chromosome-negative (Ph-) acute lymphoblastic leukemia in second or greater relapse or whose disease has progressed following two or more treatment lines of anti-leukemia therapy.  
**CMC Lead:** Janice Brown, Branch II/DNDQA1/ONDQA  
**Chief, Branch II:** Sarah Pope Miksinski, Ph.D., DNDQA1/ONDQA  
**Review team recommendation:** Team review  
 CMC reviewers: Xiao-Hong and Debasis Ghosh  
 Biopharm reviewer: John Duan  
 Yes                      No  
**ONDQA Fileability:**                      X                        
**Comments for 74-Day Letter**                                            X

**CONSULTS/ CMC RELATED REVIEWS**

Consult	Comment
Biopharm	Assigned to John Duan, Ph.D.
CDRH	Not Applicable
EA	Categorical Exclusion requested
EES	Inspection request was submitted on 03-Aug-2011
DMEPA	Labeling consult request will be sent as part of DHP request.
Methods Validation	Not needed
Microbiology	Assigned to Vinnie Pawar, Ph.D.
Pharm-Tox	Determined by primary reviewer. In addition to the impurities/degradation products in the drug product, the sponsor submitted a toxicological summary of the excipient, Sphingomyelin

## SUMMARY

Marqibo is a kit containing 3 drug product components that are compounded by the pharmacist to produce a 0.16 mg/mL Vincristine Sulfate Liposomes Injection (VSLI) drug product. The compounding process essentially loads the empty liposomes with vincristine sulfate. The VSLI drug product is then diluted into an I.V. bag containing 5% dextrose injection or 0.9% sodium chloride injection then administered to the patient by intravenous infusion over 60 minutes.

This 505(b)(2) application relies on the FDA's finding of safety and effectiveness of Oncovin (vincristine sulfate) marketed by Eli Lilly Pharmaceuticals (NDA 014103). Oncovin® (vincristine sulfate injection, USP) is no longer distributed in the U.S. and as a result of not being manufactured, is no longer a listed drug. Talon is referencing data from Oncovin NDA on the genotoxicity / mutagenicity potential of vincristine as part of the reproductive toxicity assessment of Marqibo®. Additionally, Talon does not have the right of reference to statements appearing in the Oncovin® (vincristine sulfate injection) label that are required for use in the proposed Marqibo® package insert label that include: boxed warnings, dosage and administration, contraindications, warnings and precautions, drug interactions, and overdose.

The applicant's vincristine sulfate injection formulation is based on the Eli Lilly's Oncovin formulation and Hospira Vincristine Sulfate Injection USP, 1 mg/1 mL and 2 mg/2 mL, approved under ANDA 71-484 and ANDA 71-559, respectively (see item 10 below for a comparison of the applicant's and Hospira vincristine sulfate injection formulations).

Marqibo was initially submitted as a 505(b)(2) NDA (NDA 21-600) in March 2004 by Inex Pharmaceuticals, Burnaby, British Columbia, Canada (now Tekmira Pharmaceuticals). Tekmira received a not-approval letter on January 14, 2005. Hana Biosciences, Inc. (now Talon Therapeutics, Inc) acquired development rights to Marqibo® on May 6, 2006. All pending FDA requests for additional information were submitted in various IND submissions submitted by Talon in 2010 and 2011 as a basis for submitting the current NDA. With the exception of the acceptance limit for the lipid ratio of SCLI (b) (4), the deficiencies have been addressed. Justification of the lipid ratio is included in the Sphingomyelin/Cholesterol Liposomes Injection pharmaceutical development section.

The rationale for developing a liposomal encapsulation of vincristine is the potential to enhance the delivery of conventional vincristine to tumor cells by sustaining a slow drug release, and to increase accumulation at the tumor, resulting in prolonged exposure of the drug to tumor cells. Liposomes can selectively accumulate at tumor sites because the tumor blood vessels have "pores" or "defects" through which the liposomes can pass.

Although VSLI is administered IV, almost all of the VCR (>97%) is initially encapsulated within the sphingomyelin-based liposomal carrier and not immediately available for cellular uptake. The liposomal carrier component of VSLI is small (b) (4) and has been shown to prolong the circulation time of encapsulated vincristine and to increase extravasation into tumors interstitium as well as to slow release vincristine. Prolonged exposure of cells to vincristine has been shown to enhance the in vitro cytotoxicity of the drug. This is presumably due to the fact

that at longer exposure times, a greater proportion of the cells will have passed through mitosis, where vincristine exerts its cytotoxic effects.

Vincristine is a cell-cycle-specific agent that arrests cell division in the M-phase by binding specifically with tubulin, a protein component of cell microtubules. This binding alters the tubulin polymerization equilibrium, resulting in altered microtubule structure and function. At low intracellular concentrations, VCR stabilizes the spindle apparatus, preventing chromosome segregation and resulting in metaphase arrest and inhibition of mitosis. At higher intracellular concentrations, disruption and total depolymerization of microtubules is observed.

VSLI is being developed, under the Fast Track program and has received an Orphan drug designation.

## MARQIBO® KIT

- 1.0 Vincristine Sulfate Liposomes Injection (VSLI) is a liposomal formulation of vincristine in which the drug is encapsulated in a liposome comprised of sphingomyelin (SM) and cholesterol (Chol). The Marqibo® Kit components are listed in table 1.

**Table 1: Components of the Marqibo Kit**

<b>Drug Product Component</b>	<b>Description</b>	<b>Functional Aspect</b>
Vincristine Sulfate Injection, USP (5 mg/5 mL) (VSI)	Solution	Contains the active ingredient (drug substance), Vincristine Sulfate USP
Sphingomyelin/Cholesterol Liposomes Injection (103 mg/mL) (SCLI)	Suspension	Liposome component (no active ingredient)
Sodium Phosphate Injection (14.2 mg/mL) (SPI)	Solution	Buffer diluent (no active ingredient)
One Flootation Ring	NA	Keeps vial upright. Fits around sodium phosphate vial during incubation in the water bath
One Marqibo (vincristine sulfate liposomes injection) Overlabel for Sodium Phosphate Injection Constitution Vial		
One Infusion Bag Label		
One Package Insert		

- 2.0 The drug product, vincristine sulfate liposomes, is compounded by the pharmacist by mixing vincristine sulfate and sphingomyelin/cholesterol liposomes with the sodium phosphate buffer and incubating the resulting mixture in a water bath at 65°C for 10 minutes (see 3.0 for the compounding procedure). All the components needed to compound the vincristine liposomes are contained in the Marqibo kit. The VSLI drug product is diluted into an I.V. bag containing 5% dextrose injection or 0.9% sodium chloride injection then administered to the patient by intravenous infusion within 12 hours of the start of constitution.

- 3.0 Marqibo® (vincristine sulfate liposome injection, 0.16 mg/mL) is compounded at the dispensing pharmacy. The abbreviated compounding procedure (omitting labeling) consists of the following steps:
1. Withdraw 1.0 mL of Sphingomyelin/Cholesterol Liposome Injection and inject into the Sodium Phosphate Injection Constitution Vial.
  2. Withdraw 5.0 mL of Vincristine Sulfate Injection and inject into the Sodium Phosphate Injection Constitution Vial.
  3. Invert 5 times.
  4. Attach flotation ring around neck of Sodium Phosphate Injection Constitution Vial.
  5. Place the Sodium Phosphate Injection Constitution Vial containing Vincristine Sulfate Injection, Sphingomyelin/Cholesterol Liposomes Injection, and Sodium Phosphate Injection into the 65°C water bath for 10 minutes.
  6. At the end of the 10 minute constitution period, inject appropriate patient dose as calculated based on the patient's BSA into an I.V. bag containing 5% dextrose injection or 0.9% sodium chloride injection to a final volume of 100 mL.

4.0 CHARACTERIZATION – Characterization studies of constituted VSLI are summarized below.

- 4.1 Liposome Morphology by freeze-fracture electron microscopy (see figure 25). The particles are spherical and of homogeneous size with average diameter of (b) (4) nm; (b) (4) of particles were within the range (b) (4). No changes in particle morphology are observed before and after loading with vincristine.

**Figure 25** **Freeze-Fracture Electron Micrograph of VSLI**



4.2 An interesting description of the vincristine encapsulation chemistry is reproduced below from section 3.2.P.2.3.3.



4.3 Robustness studies were performed on the constitution process and the constitution time and temperature were found to influence vincristine sulfate loading (see table 26).

**Table 26**                      **Influence of Constitution Process Parameters on Vincristine-Loading Efficiency**

Process Stage Number	Procedure Evaluated	Result	Consequential Changes to the Constitution Process
(b) (4)			

4.4 An in vitro release (IVR) method used to evaluate liposomal vincristine release profiles is also used to assess product performance and measure the consistency of manufacture of

the drug components. This method determines the concentration of vincristine released in the presence of 1-butanol. Released vincristine is isolated from the liposomes by ultrafiltration and quantitated by an isocratic, reverse phase HPLC method with UV detection. Correlation between the IVR method test acceptance criteria and the vivo pharmacokinetic results along with the method validation should be evaluated by the ONDQA biopharm reviewer.

5.0 The manufacturing flow diagram for the Marqibo is reproduced in attachment 2.

6.0 SPECIFICATIONS - The Vincristine Sulfate Liposomes Injection (0.16 mg/mL) (VSLI) specification is listed in table 2 below.

Table 2: Proposed VSLI Specification

Test	Analytical Procedure	Acceptance Criteria
Description	NT 100-1549	White to off-white, translucent suspension, essentially free of visible foreign matter and aggregates
Identification Vincristine Sulfate	NT 100-1553 (HPLC)	(b) (4)
Vincristine Sulfate Content Total Free	NT 100-1553	
Related Compounds <span style="background-color: #cccccc; padding: 2px;">(b) (4)</span> Any other compound Total	NT 100-1500 (HPLC)	
pH	USP <791> (NT 100-1548)	
Osmolality	USP <785> (NT 100-1550)	
Particle Size, Mean Diameter	NT 100-1555	
Particle Size, Distribution Distribution 25 (D25) Distribution 90 (D90)	NT 100-1555	
Particulate Matter ≥ 10 µm ≥ 25 µm	USP <788> Microscopic Method	
Volume in Container	USP <1> (NT 100-1546)	
In Vitro Release 0.5 hours 6 hours 24 hours 72 hours	NT 100-1552 (HPLC)	
Bacterial Endotoxins	USP <85> Gel-clot technique	

Abbreviations: D25 = 25th percentile size distribution; D90 = 90th percentile size distribution; EU = endotoxin units; HPLC = high performance liquid chromatography; NMT = not more than; NLT = not less than;

## 7.0 STABILITY

7.1 The expiry dating assigned to the Marqibo Kit is the date on which the first drug product component with the shortest remaining expiry dating at the time the Marqibo Kit is packaged.

## 7.2 IN-USE STABILITY STUDIES

7.2.1 Studies were conducted to evaluate the in-use stability and compatibility of VSLI admixtures prepared with 0.9% Sodium Chloride Injection or 5% Dextrose Injection contained in (b) (4) IV infusion bags. IV bags were stored at 2 to 8°C for up to 1 week or at room temperature (exposed to ambient light) for up to 48 hours. Since admixtures are administered in a hospital setting and the proposed labeling indicates that administration should be within 12 hours of the start of constitution, only the room temperature/ambient light studies represent actual use. Testing included description, total vincristine sulfate, free vincristine sulfate, related compounds, pH, osmolality, particle size, and the leachable (b) (4) from (b) (4) IV bags. Admixtures in both 5% dextrose and 0.9% sodium chloride met the acceptance criteria when held for 48 hours at room temperature in ambient light. In 5% Dextrose solution and 0.9% sodium chloride, the (b) (4) levels approached the proposed limit of NMT (b) (4) with a result of (b) (4) respectively.

7.2.2 In the long-term (2-8°C) and accelerated (25°C) stability studies, freshly constituted VSLI was tested at each time point. The stability of constituted VSLI was tested after 24 hours storage in the constitution vial (at 2-8°C or 25°C) and as a diluted VSLI admixture in IV bags (at 2-8°C or room temperature). Under the long-term conditions, all test results were within the specification limits. (b) (4) was the primary VSLI degradant observed; no other impurities were observed above (b) (4)

## **VINCRISTINE SULFATE INJECTION**

### **DRUG SUBSTANCE**

8.0 Fine Chemicals Corporation provided a letter of authorization dated 21-Dec-2010 allowing the agency to reference the confidential information in DMF 4561 for vincristine sulfate. DMF 4561 was reviewed on 01/10/2005 and found acceptable.



12.0 IMPURITIES - Listed below are the impurities in VSI drug product. Impurity limits meet the USP limit for Vincristine Sulfate Injection.

Table 5: Potential Impurities in VSI

Potential Impurity	Potential Source
(b) (4)	

12.1 Since the listed drug is no longer available and the applicant has stated that their formulation is also based on Hospira's product, consider requesting a comparative impurity analysis with Hospira's drug product.

13.0 SPECIFICATIONS - The vincristine sulfate injection drug product specification is reproduced in table 6.

Table 6: VSI Specification

Test	Analytical Method	Acceptance Criteria
Description	V100-FP (Visual)	A clear, colorless solution
Identification	USP (TLC)	Meets USP requirements
Assay	USP (HPLC)	(b) (4)
Related Compounds	USP (HPLC)	
<div style="background-color: #cccccc; width: 100px; height: 15px; margin-bottom: 5px;"></div> Any other individual Total		
pH	USP <791>	
Volume in Container	USP <1>	
Particulate Matter ≥ 10 μm ≥ 25 μm	USP <788> Light obscuration method	
Sterility	USP <71>	
Bacterial Endotoxins	USP <85>	

14.0 CONTAINER CLOSURE - VSI container closure system is summarized in table 7.

Table 7: Summary of Container Closure System for VSI

Component	Description	Supplier/Manufacturer Name and Address	DMF
(b) (4)			

15.0 DRUG PRODUCT STABILITY STUDIES

15.1 The applicant submitted 24 months of long term stability (2 to 8°C) data for 8 lots (six clinical study lots and 2 commercial lots) of Vincristine Sulfate Injection USP (5 mg/5 mL) manufactured at the Mulgrave facility of Hospira; however, only five lots were manufactured using the container-closure intended for marketing. Four lots were also placed on accelerated stability at 25°C/60% relative humidity (RH), only three lots were manufactured using the container-closure intended for marketing. Stability results that support the proposed expiry are summarized in table 5.

Table 5 – Stability results for VSI filled in the proposed container closure.

Lot no.	Amount of data	Result
S029602X	24 months long term data at 2-8°C	All results met the proposed acceptance criteria
T019602A	24 months long term data at 2-8°C	All results met the proposed acceptance criteria
T029602XA	24 months long term data at 2-8°C	All results met the proposed acceptance criteria
	6 months accelerated data at 25°C/60%RH	<b>Failed</b> (b) (4) <b>limit at 3 mo.</b> <b>Failed Assay limit at 6 mo.</b>
U029602XA	24 months long term data at 2-8°C	All results met the proposed acceptance criteria
	6 months accelerated data at 25°C/60%RH	<b>Failed</b> (b) (4) <b>limit at 3 mo.</b> <b>Failed Assay limit at 6 mo.</b>
W019602A	24 months long term data at 2-8°C	All results met the proposed acceptance criteria
	6 months accelerated data at 25°C/60%RH	<b>Failed</b> (b) (4) <b>limit at 6 mo.</b>

- 15.2 The applicant has proposed shelf life of 24 months when stored at 2 to 8°C. According to ICH Q1A(R2), if significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed shelf life should be based on the real time data available from the long term storage condition.
- 15.3 The VSI stability specification is reproduced below.

Table 6: VSI Stability Specifications

Test	Analytical Procedure	Acceptance Criteria
Description	Visual	A clear, colorless solution
pH	USP <791>	(b) (4)
Assay	USP	
Related Substances (b) (4) Any other individual Total	USP	
Volume in Container	USP <1>	
Particulate Matter ≥ 10 µm ≥ 25 µm	USP <788>	
Sterility	USP <71>	
Bacterial Endotoxins	USP <85> Gel Clot	

- 15.4 Freeze-thaw studies: A freeze-thaw study was performed on VSI. The drug product was cycled 3 times from 25°C to -20°C (48 hours at each temperature, upright orientation). Drug product testing was not performed due to container breakage and product leakage problems. Labeling includes a statement that the product should not be frozen.
- 15.5 Photostability – VSI was exposed to light (average 14,000 lux) and tested for potency and related substances after 0, 2, 4 and 7 days. Under these conditions, the potency remained within specification. The related substances levels increased significantly over the 7 days, but remained within specification. The applicant states that the product is light sensitive.

**SPHINGOMYELIN/CHOLESTEROL LIPOSOME INJECTION (SCLI)** - Cangene Corporation provided a letter of authorization dated 30-Mar-2011 allowing the agency to reference the confidential information in DMF 16557 for SCLI.

## 16.0 COMPOSITION

- 16.1 SCLI is composed of sphingomyelin and cholesterol at a molar ratio of 58:42. At this ratio, sphingomyelin and cholesterol form a highly stable liposomal

membrane with low permeability, maintaining liposome integrity during the constitution to VSLI at 65°C and providing sustained release of encapsulated vincristine at approximately 37°C (body temperature). (b) (4)

16.2 The composition of the SCLI is reproduced in the table 7 below.

Table 7: Quantitative Composition of SCLI

Component	Quality Standard	Function	Quantity per Milliliter (mL)	Quantity per Vial
Sphingomyelin	Internal DMF (b) (4)	Functional liposome excipient	73.5 mg	73.5 mg
Cholesterol HP	NF DMF (b) (4)	Functional liposome excipient	29.5 mg	29.5 mg
Citric Acid, (b) (4)	USP	(b) (4)	33.6 mg	3.6 mg
Sodium Citrate, (b) (4)	USP		35.4 mg	35.4 mg
(b) (4)	USP		< 0.10% (v/v)	< 0.10% (v/v)
(b) (4)	USP			
(b) (4)	NF			
<b>Total Volume</b>			1 mL	1 mL

16.3 Both sphingomyelin (b) (4) and cholesterol HP (b) (4) are from animal origin. The manufacture's certified that controls were established for materials of animal origin regarding TSE/BSE. The following FDA guideline <http://frwebgate.access.gpo.gov/cgi-bin/get-cfr.cgi?TITLE=9&PART=94&SECTION=18&TYPE=TEXT> is listed to help reviewers with the agency's requirements for animal sourced material.

16.4 All excipients except sphingomyelin are compendial.

16.5 Sphingomyelin is a novel excipient and has not previously been used as an FDA approved product. The applicant performed two SCLI empty liposome toxicology studies. The P/T reviewer has been notified of this study.

17.0 SCLI manufacturing flow diagram is reproduced in attachment 2.

## 18.0 IMPURITIES

### 18.1 Sphingomyelin Process-Related Impurities – (b) (4)

(b) (4) Impurities are controlled at the excipient specification stage (see NDA section 3.2.A.3 for batch analysis for different lots of sphingomyelin used to make drug product).

### 18.2 Cholesterol Process-Related Impurities - (b) (4)

18.3 Based on forced degradation studies (b) (4) is the primary degradant of SCLI. It is observed under all forced degradation conditions and is seen under accelerated stability conditions. For this reason, SCLI is tested for (b) (4) in the primary stability studies.

19.0 SPECIFICATIONS - The SCLI drug product specification is reproduced in table 8 below.

Table 8: Proposed SCLI Specification

Test	Analytical Method	Acceptance Criteria
Description	STM 705308	White to off-white homogeneous opalescent suspension, essentially free of visible foreign matter and aggregates
Identification Sphingomyelin	STM 705313	(b) (4)
Cholesterol	STM 705314	
Content Sphingomyelin	STM 705313	
Cholesterol	STM 705314	
Lipid Ratio	Calculation	
Lipid Degradation Products (b) (4)	M1162	
Unspecified Degradation Products		
pH	USP <791> (STM 501000) <sup>c</sup>	
Osmolality	USP <785> (STM 520105) <sup>c</sup>	
Particle Size, Mean Diameter	STM 705311	

Test	Analytical Method	Acceptance Criteria
Particle Size, Distribution 25 (D25) Distribution 90 (D90)	STM 705311	(b) (4)
Residual (b) (4)	STM 705301	
Particulate Matter ≥ 10 µm ≥ 25 µm	USP <788> Microscopic test	
Volume in Container	USP <1> (STM 705309)c	
Sterility	USP <71> (STM 520027)c	
Bacterial Endotoxins	USP <85> (Gel clot)	

19.1 Consider requesting acceptance criteria for unspecified degradation products.

20.0 CONTAINER CLOSURE – SCLI container closure system is summarized in table 9.

Table 9: Summary of Container Closure System for SCLI

Component	Description	Supplier Name and Address	DMF
(b) (4)			

## 21.0 DRUG PRODUCT STABILITY STUDIES

21.1 The applicant submitted 24 months of long term stability (2 to 8°C) data for 2 lots and 18 month data for one lot manufactured by the Cangene Corporation (Cangene) at the commercial (b) (4) production scale with a (b) (4) target fill. A minimum of 6 month accelerated data was provided for three batches. The applicant submitted a total of 11 lots to support the proposed expiry and includes supportive data. Both long term and accelerated results met the proposed acceptance criteria.

(b) (4)

(b) (4)

21.2 The proposed expiry period for SCLI is (b) (4)

21.3 Freeze-thaw studies: The drug product was cycled 3 times for 2 days at -25°C (±5°C) and 2 days of refrigeration at 5°C (2-8°C). Labeling included a statement that the product should not be frozen.

21.6 Photostability – SCLI was exposed to light conditions of 1.2 million lux hours and 200 watt hours/m2 and tested. Light-exposed samples failed (b) (4) and particle size. The applicant states that the product is light sensitive.

A second photostability study was performed to determine the effect of minimal exposure of SCLI to light for brief periods of time such as during manufacture and VSLI constitution. Vials of SCLI stored horizontally were exposed to ambient room lighting (~550 lux) and room temperature (~23°C) for 24 and 48 hours. Samples exposed to ambient lighting for 24 and 48 hours met the proposed acceptance criteria.

**SODIUM PHOSPHATE INJECTION (SPI)** – Jubilant HollisterSteir LLC provided a letter of authorization dated 20-Apr-2011 allowing the agency to reference the confidential information in DMF 4030 for SPI.

22.0 COMPOSITION - (b) (4)  
The composition of the SPI is reproduced in the table 10 below.

Table 10: Quantitative Composition of SPI

Component	Quality Standard	Function	Quantity per Milliliter (mL)	Quantity per Vial
Dibasic Sodium Phosphate, (b) (4)	USP	(b) (4)	14.2 mg	355.0 mg
Sodium Chloride	USP		9.0 mg	225.0 mg
(b) (4)	USP		(b) (4)	
	NF			
<b>Total Volume</b>			1 mL	25 mL

20.0 SPI manufacturing flow diagram is reproduced in attachment 4.

21.0 IMPURITIES – The applicant has not identified any impurities not control by compendial monographs for Dibasic Sodium Phosphate (b) (4) USP, Sodium Chloride USP, (b) (4)

22.0 SPECIFICATIONS - The SCLI drug product specification is listed in table 11.

Table 11 - Proposed Specification for Sodium Phosphate Injection

Test	Analytical Method <sup>a</sup>	Acceptance Criteria
Description	M1282	Clear, colorless solution, essentially free of visible particulates
Identification Sodium	USP <191> (M5105)	(b) (4)
Phosphate	USP <191> (M5105)	
Content Sodium Phosphate Sodium Chloride	M1154 <sup>b</sup> M1153 <sup>c</sup>	
pH	USP<791> (M1149)	
Osmolality	USP<785> (M1150)	
Particulate matter ≥ 10 μm ≥ 25 μm	USP <788> (light obscuration)	
Sterility	USP <71>	
Bacterial endotoxins	USP <85> (gel clot)	

Abbreviations: NMT = not more than; SPI = Sodium Phosphate Injection (14.2 mg/mL); USP = United States Pharmacopeia.

- <sup>a</sup> Testing facilities may assign their own unique document numbers to the compendial method for control purposes.
- <sup>b</sup> USP Monograph Sodium Phosphates Injection (Assay for Dibasic Sodium Phosphate Test).
- <sup>c</sup> USP Monograph Sodium Chloride Injection (Assay Test).

23.0 CONTAINER CLOSURE – SPI container closure system is summarized in table 12.

Table 12: Summary of Container Closure System for SPI

Component	Description	Supplier/Manufacturer Name and Address	DMF
(b) (4)			

Component	Description	Supplier/Manufacturer Name and Address	DMF
(b) (4)			

## 24.0 DRUG PRODUCT STABILITY STUDIES

24.1 The applicant submitted between 24 and 48 months of long term stability (2 to 8°C) data for 9 lots of SPI manufactured at Jubilant HollisterStier (JHS), Spokane, Washington, at production scales of (b) (4) and packaged in the proposed commercial molded glass vial. (b) (4)

(b) (4) Six months of accelerated data was submitted for all 9 lots. The amount of stability data submitted for lots 6579W, 7044 and C0069 are 24 months, 48 months, and 24 months, respectively. With the exception of one failure at accelerated conditions, both long term and accelerated results met the proposed acceptance criteria. The failure was reported for appearance at 6 months at 25°C in Lot 6480 due to (b) (4)

24.2 The proposed expiry period for SPI is (b) (4)

24.3 Heat Stress Studies - Additional testing at the extreme stress conditions of 40°C/75% RH was performed on 5 lots of SPI packaged in the proposed commercial molded glass vial. All vials remained intact for 1 month. Notably at 2 months, most vials started to (b) (4) (b) (4) also increased from the initial sample and all subsequent timepoints. The increase in (b) (4) levels may be significant to the stability of the liposomes during pharmacy compounding.

24.4 Freeze-thaw studies: One lot of SPI drug product was cycled from -20 to 40°C for 3 cycles (48 hours at each condition with equilibration at 25°C/60% RH between extremes). After 3 freeze-thaw cycles, the SPI met the appearance, sodium phosphate content, sodium chloride content, particulate matter, pH, osmolality, or container closure integrity limits. Labeling included a statement that the product should not be frozen.

24.5 Photostability: The applicant did not perform photostability testing.

25. DMF - The following DMFs were referenced.

Supporting DMFs:

DMF	TYPE	HOLDER	ITEM REFERENCED
(b) (4)			

DMF	TYPE	HOLDER	ITEM REFERENCED
(b) (4)			

26. Environmental Assessment: The applicant has submitted a claim for categorical exclusion under 25.31(b) which states that use of this product will not cause the concentration of the drug substance active moiety to be one part per billion (1 ppb) or greater at the point of entry into the aquatic environment.
27. Establishment Evaluation: A full list of facilities involved in the manufacture, packaging and testing is reproduced in attachment 1.

**CRITICAL ISSUES FOR REVIEW**

1. The in vivo rate of drug release is critical to the safety and efficacy of this product. If the vincristine release were immediate, the patient would be exposed to high levels of the drug. Alternatively, if the vincristine were not released from the liposomes, appropriate dosing would not be achieved and efficacy would be compromised. An in vitro release (IVR) method is used to evaluate liposomal vincristine release profiles. Correlation between the IVR method test acceptance criteria and the vivo pharmacokinetic results along with the method validation should be evaluated by the ONDQA biopharm reviewer.
2. Vincristine Sulfate
  - a. The applicant states that the impurity profile for vincristine sulfate and vincristine sulfate injection complies with the compendial monograph. The submission did not include detailed information on the impurity profile of their product. Since the listed drug is no longer available and the applicant has stated that their formulation is also based on Hospira's product, consider requesting a comparative impurity assessment with Hospira's drug product.

- b. Vincristine sulfate is temperature sensitive and must be stored under refrigeration. Based on accelerated stability data, storage at room temperature (25°C) resulted in elevated levels of (b) (4) at the specification limit of (b) (4) at the 3 months test station. (b) (4) is the only degradation product of VSLI for which impurity levels exceed the qualification threshold.

Vial breakage occurs when the product is exposed to freeze-thaw conditions. The proposed labeling includes a statement “Do Not Freeze” .

- c. Vincristine sulfate injection is light sensitive.
  - d. Vincristine sulfate injection failed accelerated stability testing; therefore, shelf life should be based on long term data. Since the 3 month test station failed accelerated conditions (25°C), the in-use studies should address the stability of the short term excursions during the constitution procedure where the product is held at 65°C for 10 minutes and the 12 hour admixture hold time during patient administration. These studies were included in the submission.
3. SCLI (Liposomes)
- a. Sphingomyelin is a novel excipient and has not previously been used as an FDA approved product. The applicant performed two SCLI empty liposome toxicology studies to qualify this excipient.
  - b. SCLI can not be frozen. After 3 freeze-thaw cycles, the SCLI failed to meet the acceptance criteria for visual appearance, osmolality and particle size.
  - c. SCLI is light sensitive. Light-exposed samples failed (b) (4) and particle size.
4. Sodium Phosphate Injection – Vials containing the drug product (b) (4) when exposed to elevated temperature (40°C) for two months. (b) (4) also increased from the initial sample and all subsequent timepoints. The increase in (b) (4) levels may be significant to the stability of the liposomes during pharmacy compounding.

Attachment 1: Facility information

Drug Product Component [Sphingomyelin/Cholesterol Liposome Injection, Cangene]

Name and Address	Responsibilities	Contact Information
Cangene Corporation 155 Innovation Drive Winnipeg, Manitoba R3T 5Y3 Canada Facility Establishment Identifier: 3003153579 DMF: DMF (b) (4)	Manufacture and Release testing	Chris Downey Manager, Quality Assurance, Compliance and Validation Tel: 204.275.4237 Fax: 204.269.4298 e-mail: cdowney@cangene.com

Drug Product Component [Sodium Phosphate Injection, Jubilant HollisterStier]

Name and Address	Responsibilities	Contact Information
Jubilant HollisterStier LLCa 3525 North Regal Street Spokane, WA 99207-5788 USA Facility Establishment Identifier (FEI): 3010477 DMF: 4030	Manufacture and Release testing	Brian Enright Director, Regulatory Affairs Tel: 509.489.5656 Fax: 509.484.4320 e-mail: benright@jhs.jubl.com

Drug Product Component [Vincristine Sulfate Injection, Hospira]

Name and Address	Responsibilities	Contact Information
Hospira Australia Pty Ltd 1 Lexia Place Mulgrave Victoria 3170 Australia FEI: 3001174929	Vincristine Sulfate Injection - Manufacturing (including bulk packaging), release and stability testing	Justine Mann Site Quality Director Tel: 61 3 8541 5242 Fax: +61 3 8541 5786 Email: justine.mann@hospira.com Justin Daly VP Manufacturing Operations Tel: + 61 3 8541 5314 Fax: + 61 3 8541 5081 Email: <a href="mailto:justin.daly@hospira.com">justin.daly@hospira.com</a>

Attachment 1: Facility information – Continued

Drug Substance [Vincristine Sulfate, Fine]

Name and Address	Responsibilities	Contact Information
Fine Chemicals Corporation (Pty) Limited 15 Hawkins Avenue Epping 1 7460 Cape Town South Africa FDA Federal Establishment Identifier (FEI): 3002806969 DMF : 4561	Manufacture, Release and Stability testing	Dr. Michiel Loedolff Technical Operations Tel: +2721-530-8106 Fax: +2721-531-1458 Email: michiel@fcc.co.za

Excipients [Cholesterol HP, (b) (4)]

Name and Address	Responsibilities	Contact Information
(b) (4)	Manufacture, Release and Stability testing	(b) (4)

Excipients [Sphingomyelin, (b) (4)]

Name and Address	Responsibilities	Contact Information
(b) (4)	Manufacture, Release and Stability testing	(b) (4)

Testing Laboratory

Name and Address	Responsibilities	Contact Information
Nucro-Technics 2000 Ellesmere Road, Unit #16 Scarborough, Ontario M1H 2W4 Canada FEI: 3002807768	Release and Stability testing	Contact: Charles Lee Chemistry Department Tel: 416.438.6727 Fax: 416.438.3463 Email: clee@nucro- technics.com

Attachment 1: Facility information – Continued

Testing Laboratory

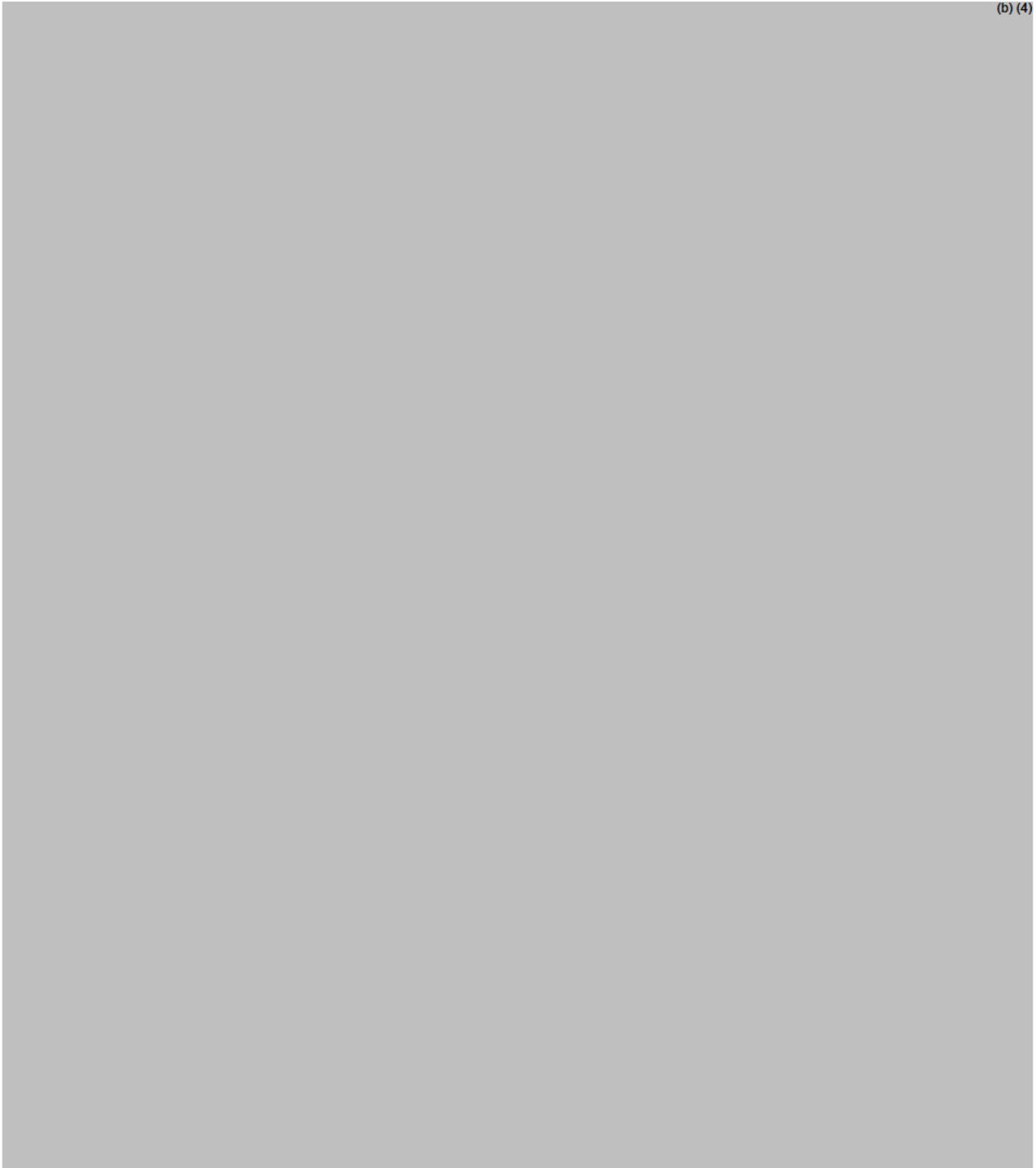
Name and Address	Responsibilities	Contact Information
PPD Development 8500 Research Way Middleton, WI 53562-3581 USA FEI: 2129896	Release and Stability testing	Magdalena Mejillano Vice President, GMP Laboratory Services Tel: 608.827.9400 Fax: 608.827.8807 e-mail: Magdalena.Mejillano@ppdi.com

Packaging and Labeling [Marqibo Kit]

Name and Address	Responsibilities	Contact Information
Anderson Packaging, Inc. 1635 New Milford School Road Rockford, IL 61109 USA Facility Establishment Identifier (FEI): 1424506	Packaging and Labeling	Steve McNett Vice President of Quality Tel: (815) 484-8919 Email: SMcNett@andpkg.com

Attachment 2: Marqibo Kit Manufacturing Flow Diagram

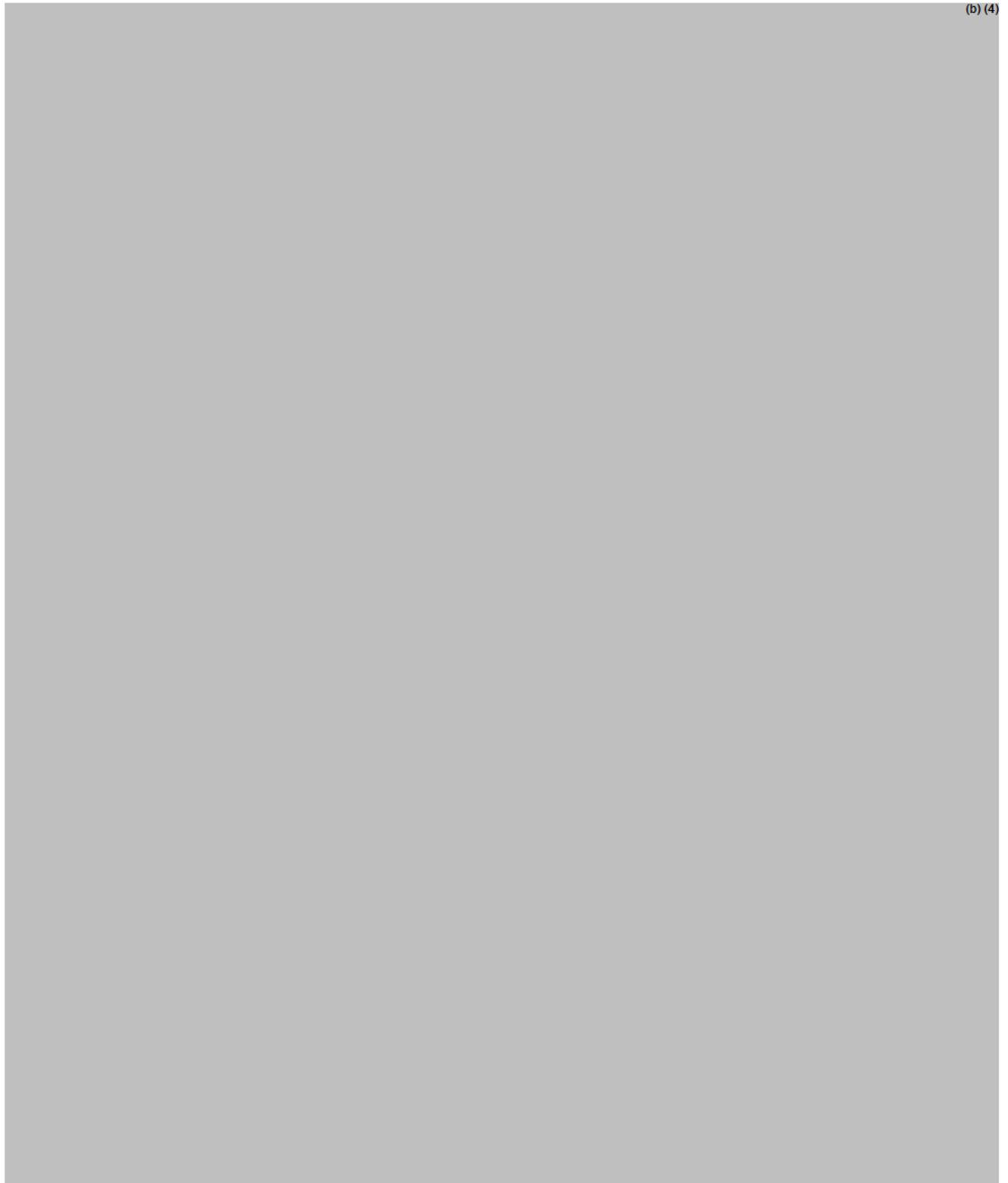
**Figure 1**                      **Marqibo Component Labeling and Kit Assembly**



(b) (4)

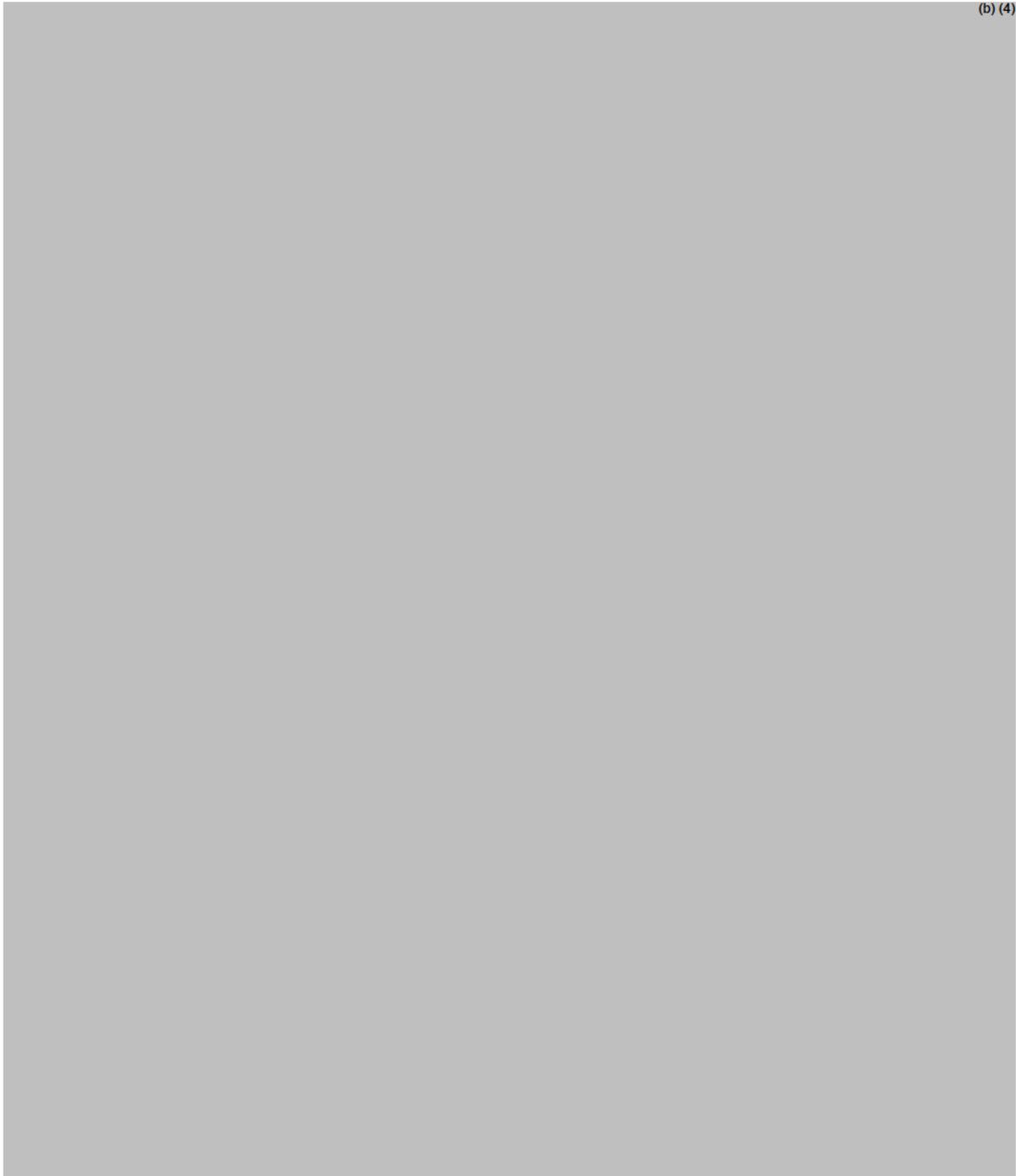
Attachment 3: Vincristine Sulfate Injection Manufacturing Flow Diagram

**Figure 1**                      **VSI Manufacturing Process Flow Diagram**



Attachment 4: Sphingomyelin/Cholesterol Liposomes Injection (103 mg/mL)  
Manufacturing Flow Diagram

**Figure 1**                      **SCLI Manufacturing Process Flow Diagram**



Attachment 4: Sphingomyelin/Cholesterol Liposomes Injection (103 mg/mL)  
Manufacturing Flow Diagram - Continued

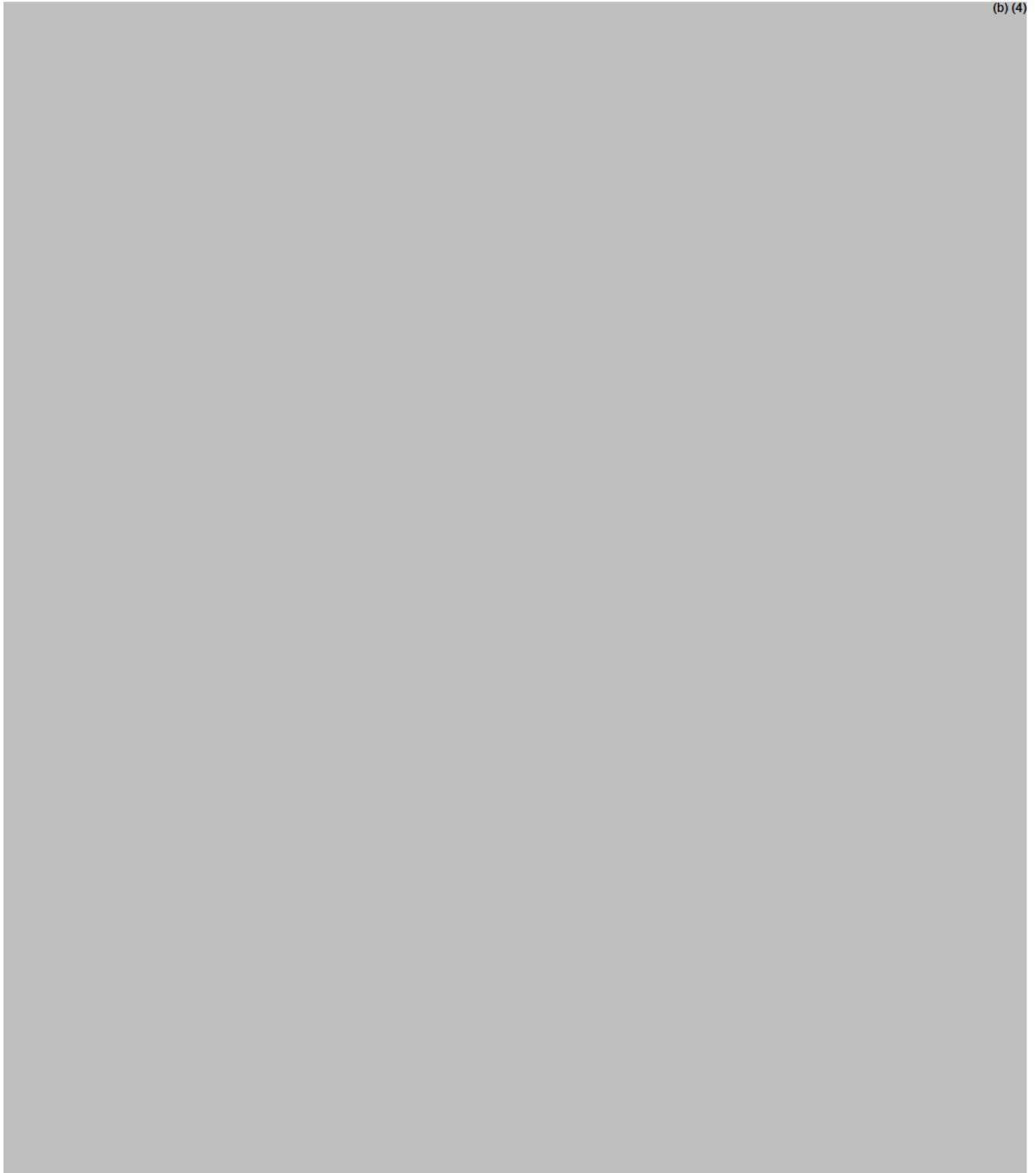
**Figure 1**                      **SCLI Manufacturing Process Flow Diagram (continued)**



(b) (4)

Attachment 4: Sphingomyelin/Cholesterol Liposomes Injection (103 mg/mL)  
Manufacturing Flow Diagram - Continued

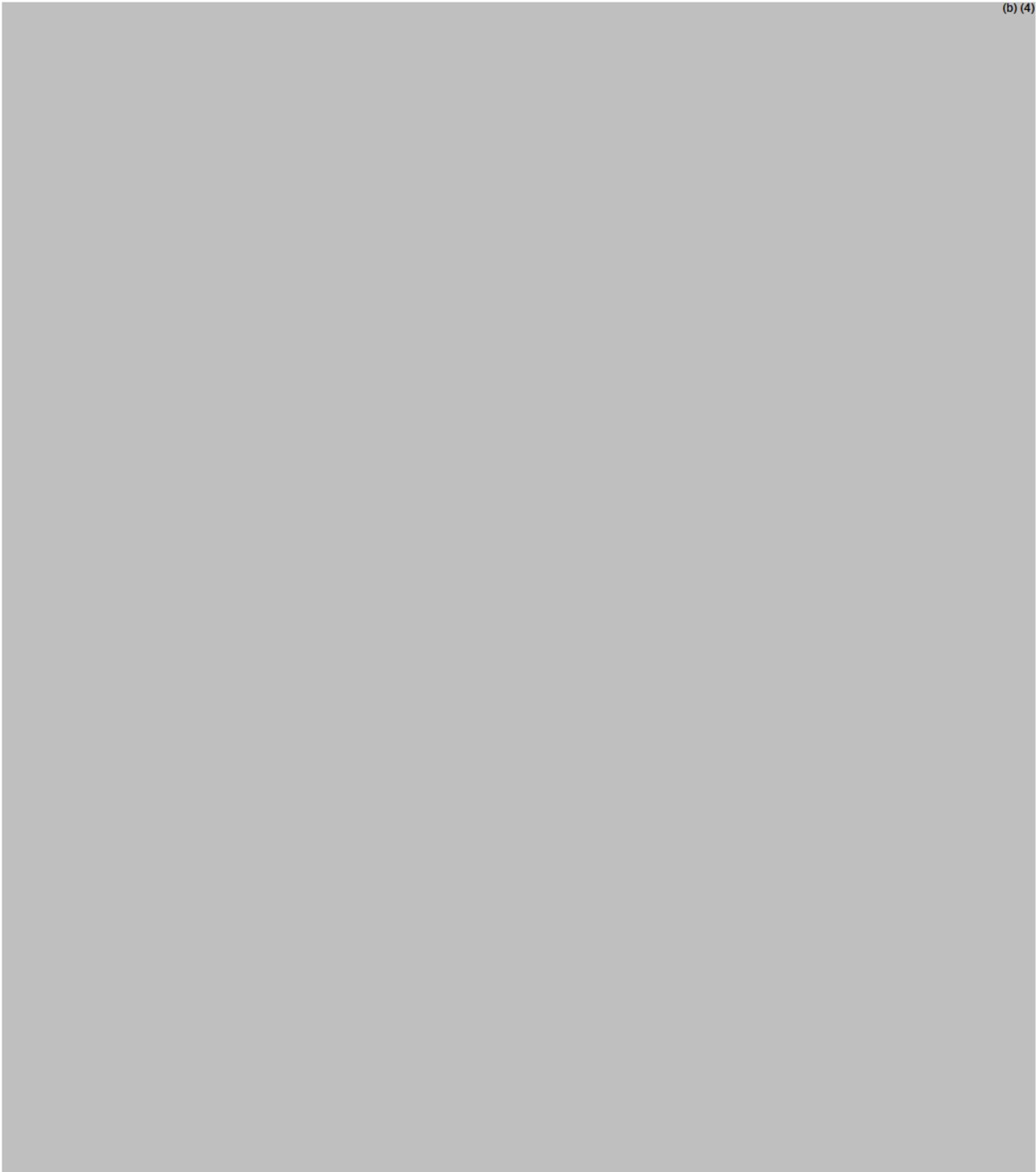
**Figure 1**                      **SCLI Manufacturing Process Flow Diagram (continued)**



(b) (4)

Attachment 5: Sodium Phosphate Injection Manufacturing Flow Diagram

**Figure 1**                      **SPI Manufacturing Process Flow Diagram**



(b) (4)

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/s/  
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JANICE T BROWN  
09/06/2011

SARAH P MIKSINSKI  
09/06/2011

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA or Supplement (ONDQA)**

<b>NDA Number:</b>	<b>Supplement Number and Type:</b>	<b>Established/Proper Name:</b>
202497	Original NDA	Marqibo (Vincristine Sulfate Liposomes Injection)
<b>Applicant:</b>	<b>Letter Date:</b>	<b>Stamp Date:</b>
Talon Therapeutics, Inc.	12-Jul-2011	12-Jul-2011

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	PARAMETER	YES	NO	COMMENT
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	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? <b>This question is not applicable for synthesized API.</b>			NA
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA or Supplement (ONDQA)**

<b>B. FACILITIES*</b>				
	<b>PARAMETER</b>	<b>YES</b>	<b>NO</b>	<b>COMMENT</b>
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		
9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

\* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

<b>C. ENVIRONMENTAL ASSESMENT</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
11.	Has an environmental assessment report or categorical exclusion been provided?	X		

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA or Supplement (ONDQA)**

<b>D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
12.	Does the section contain a description of the DS manufacturing process?	X		Referenced DMF
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Referenced DMF
14.	Does the section contain information regarding the characterization of the DS?	X		Referenced DMF
15.	Does the section contain controls for the DS?	X		Referenced DMF
16.	Has stability data and analysis been provided for the drug substance?	X		Referenced DMF
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	
<b>E. drug product (dp)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		Expiry will be determined by primary reviewers in ONDQA
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA or Supplement (ONDQA)**

<b>F. METHODS VALIDATION (MV)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
29.	Is there a methods validation package?	X		

<b>G. MICROBIOLOGY</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?			Defer to micro reviewer

<b>H. MASTER FILES (DMF/MAF)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

<b>I. Labeling</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA or Supplement (ONDQA)**

<b>J. FILING CONCLUSION</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
34.	<b>IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?</b>	X		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			N.A.
36.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?		X	

*{See appended electronic signature page}*

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Janice Brown  
Pharmaceutical Assessment Lead or CMC Lead / CMC Reviewer  
Division of Pre-Marketing Assessment 1  
Office of New Drug Quality Assessment

Date: 29-Aug-2011

*{See appended electronic signature page}*

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Sarah Pope Miksinski, Ph.D.  
Chief, Branch 2  
Division of Pre-Marketing Assessment 1  
Office of New Drug Quality Assessment

Date: 29-Aug-2011

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JANICE T BROWN  
09/06/2011

SARAH P MIKSINSKI  
09/06/2011