CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202497Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

ONDQA BIOPHARMACEUTICS REVIEW

NDA 505 (b)(2)**:**	**202-497**
Submission Date:	07/12/2011, 3/14/2012, 4/10/2012
Brand Name:	Marqibo
Generic Name:	Vincristine Sulfate Liposomes Injection
Formulation:	Injection
Strength:	0.16 mg/mL
Applicant:	Talon Therapeutics
Reviewer:	John Duan, Ph.D.
Submission Type:	Original NDA

SYNOPSIS

Submission: On 7/13/2012, Talon Therapeutics submitted 505 (b)(2) NDA 202-497 Marqibo (Vincristine Sulfate) Liposomes Injection to seek the accelerated registration of their product as the single agent treatment for the indication of "the treatment of adult Philadelphia chromosome negative (Ph-) acute lymphoblastic leukemia (ALL) in second or greater relapse or in patients whose disease has progressed following two or more anti-leukemia therapies."

Review: The Biopharmaceutics review is focused on the evaluation and acceptability of the proposed in vitro release (IVR) assay and acceptance criteria.

RECOMMENDATION

ONDA-Biopharmaceutics has reviewed the provided IVR information for Marqibo and considers that the following proposed IVR method is acceptable.

IVR Method for Marqibo Liposomes Injection	
Apparatus:	Shaker-waterbath
Media:	1-Butanol in PBS 2.75%
Volume:	105 mL
Pre incubation time:	1 h
Agitation speed:	70 rpm
Temperature:	37±0.1 °C
Analytical Method for vincristine sulfate	HPLC Analysis with UV at 297nm

With respect to the proposed acceptance criteria for the IVR test, there were several communications between FDA and the Applicant [3/19/12 (IR Letter), 3/14/12 Applicant's response), and 3/26/12 (IR Letter)]. In a submission dated 4/10/12 (SN #

0012), the Applicant accepted FDA's recommendation and the final acceptance criteria for the IVR test of Marqibo are listed in the following Table.

In Vitro Release Acceptance Criteria for Marqibo Liposomes Injection	
Time	% Vincristine Sulfate Released
0.5 hours	(b) (4)
6 hours	
24 hours	
96 hours	

From the Biopharmaceutics viewpoint, NDA 202-497 for Marqibo (Vincristine Sulfate) Liposomes Injection is acceptable.

_____ _____

John Duan, Ph.D. Date
Reviewer
ONDQA Biopharmaceutics

_____ _____

Angelica Dorantes Ph.D. Date
ONDQA Biopharmaceutics Lead

cc: *NDA 202497/DARRTS*

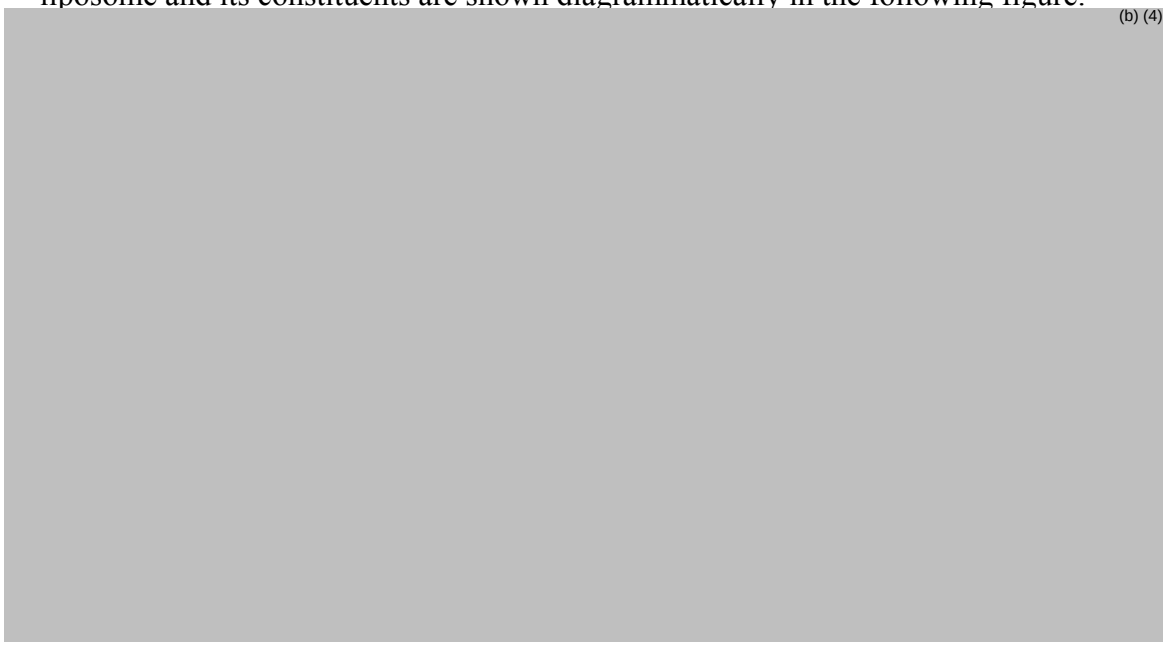
APPENDIX 1.

BIOPHARMACEUTICS ASSESSMENT

➔ **The Biopharmaceutics related information**

Proposed Drug Product: The Marqibo Kit is for the treatment of Philadelphia chromosome-negative (Ph-) acute lymphoblastic leukemia (ALL) in adults in second relapse or whose disease has progressed after 2 or more treatment lines of antileukemia therapy. The clinical dose of VSLI is 2.25 mg/m^2, administered weekly as a 1-hour IV infusion.

The biologically active ingredient of VSLI, vincristine, is a cell cycle-specific antineoplastic agent. Prolonged exposure of cells to vincristine (and other cell cycle-specific drugs) 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. The liposomal carrier component of VSLI, composed of sphingomyelin (SM) and cholesterol (Chol) and known as SM/Chol liposomes, was specifically designed to facilitate the loading and retention of vincristine, to prolong the circulation time of encapsulated vincristine, to increase extravasation into tumors, and to release the drug slowly. It was anticipated that these characteristics would result in clinically significant levels of encapsulated drug in the tumor and a long duration of exposure of tumor cells to therapeutic drug concentrations, leading to enhanced efficacy. The structures of a VSLI liposome and its constituents are shown diagrammatically in the following figure.



The vesicle lipid bilayer is composed of sphingomyelin and cholesterol at a ratio of 58:42 (mol:mol). The manufacturing target for liposome size is a 115 nm mean diameter with a specification limit of (b) (4), and vincristine is encapsulated at a drug-to-lipid ratio of (b) (4)

VSLI is designed to provide superior vincristine antitumor efficacy and tolerability in patients. The applicant claimed that the nonclinical data support that VSLI expands the desirable traits of liposome technology such as prolonged plasma circulation time, preferential accumulation of biologically active vincristine by extravasation into tumor sites, sustained release of drug at the disease sites, and reduced exposure to sensitive tissues.

➔ **The composition of the drug product**

Marqibo Kit for the Preparation of Vincristine Sulfate Liposomes Injection (Marqibo Kit) is a kit containing 3 drug product components from which Vincristine Sulfate Liposomes Injection (0.16 mg/mL) (VSLI) is constituted. VSLI is a liposomal formulation of vincristine and its composition is provided in the following table.

Source	Component	Quality Standard	Function of Source Component	Quantity per mL VSLI (mg/mL)	Quantity per vial VSLI (mg/vial)
VSI (Section 3.2.P.1 [Vincristine Sulfate Injection, Hospira])	Vincristine sulfate[a]	USP	Active ingredient	0.16	5.0
	Mannitol	USP	(b) (4)	16.1	500.0
	(b) (4)				(b) (4)
SCLI (Section 3.2.P.1 [Sphingomyelin/ Cholesterol Liposomes Injection, Cangene])	Sphingomyelin	Internal DMF (b) (4)	Functional liposome excipient	2.37	73.5
	Cholesterol HP	NF DMF (b) (4)	Functional liposome excipient	0.95	29.5
	Citric acid, (b) (4)	USP	(b) (4)	1.08	33.6
	Sodium citrate, (b) (4)	USP	(b) (4)	1.14	35.4
	(b) (4) (ethanol)	USP			(b) (4)
SPI (Section 3.2.P.1 [Sodium Phosphate Injection, Jubilant HollisterStier])	Dibasic sodium phosphate, (b) (4)	USP		11.45[c]	355.0[c]
	Sodium chloride	USP		7.26	225.0
VSI, SCLI, SPI	(b) (4)				(b) (4)
			VSLI total volume	1 mL	31 mL

Abbreviations: AR = as required; DMF = Drug Master File; HP = High Purity; NF = National Formulary; qs = quantity sufficient; USP = United Stated Pharmacopoeia; VSLI = Vincristine Sulfate Liposomes Injection (0.16 mg/mL).

[a] (b) (4)

[b] Letters of Authorization to the DMFs are provided in Section 1.4.1.

[c] (b) (4)

VSLI is constituted at the pharmacy in accordance with the package insert constitution instructions from the 3 drug product components listed in the following table.

Drug Product Component	Reference Location	Description	Functional Aspect
Vincristine Sulfate Injection, USP (5 mg/5 mL) (VSI)	Section 3.2.P.1 [Vincristine Sulfate Injection, Hospira]	Solution	Contains the active ingredient (drug substance), Vincristine Sulfate USP
Sphingomyelin/Cholesterol Liposomes Injection (103 mg/mL) (SCLI)	Section 3.2.P.1 [Sphingomyelin/Cholesterol Liposomes Injection, Cangene]	Suspension	Liposome component (no active ingredient); also known as the liposomal carrier component The liposomes themselves are referred to as sphingomyelin/cholesterol (SM/Chol) liposomes
Sodium Phosphate Injection (14.2 mg/mL) (SPI)	Section 3.2.P.1 [Sodium Phosphate Injection, Jubilant HollisterStier]	Solution	(b) (4)

➔ **In vitro release (IVR) Method Development**

In vitro release (IVR) assays are used for liposomal drug products to verify performance as part of product quality control (QC) testing. The following summarizes the development and optimization of an IVR method for determining vincristine release from VSLI upon dilution of the constituted product in a medium containing the release-promoting agent, 1-butanol.

(b) (4)

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The final procedure is outlined below.

- Samples of VSLI are diluted at a 1:21 ratio in an incubation solution of 2.75% butanol/PBS.
- Heated to 37.0 ± 0.1°C (both the concentration of 1-butanol and the water bath temperature are critical parameters that are carefully controlled).
- At selected time intervals samples are withdrawn and filtered using an ultrafiltration device.
- The amount of vincristine in the filtrate is then determined by isocratic HPLC.

➔ **The assay validation**

The validation evaluated the specificity, linearity, accuracy, precision, limits of detection and quantitation, and robustness of the method. Reproducibility (inter-laboratory precision) was evaluated between Nucro-Technics, Inc. (Nucro) Chemistry department and Inex Pharmaceuticals Corporation (INEX) Quality Control (QC) laboratory. The validation results are summarized in the following table.

TABLE Summary of Validation Results

Parameter	Acceptance Criteria	Result	Pass/Fail
	(b) (4)	(b) (4)	
Specificity			Pass
			Pass
Linearity			Pass
Accuracy			Pass
			Pass
Precision			
Repeatability			
			Pass
			Pass
			Pass
			Pass
Inter-day			
			Pass
Inter-analyst			Pass
Inter-instrument			Pass
Reproducibility			Pass

Parameter	Acceptance Criteria	Result	Pass/Fail
Range		(b) (4)	N/A
Limit of Detection			Pass
Limit of Quantitation			Pass
			Pass
			Pass
Robustness - Stability of Samples			
Total vincristine: recovery (b) (4) of initial result			
Storage at ambient temperature:		(b) (4)	
24 h			Pass
72 h			Pass
1 week			Pass
Storage at 5°C:			
24 h			Pass
72 h			Pass
1 week			Pass
Released vincristine: recovery (b) (4) of initial result			
Storage at ambient temperature for:		(b) (4)	
24 h	0.5 h IVR time point		Pass
72 h			Pass
1 week			Pass
24 h	24 h IVR time point		Pass
72 h			Pass
1 week			Pass
24 h	96 h IVR time point		Pass
72 h			Pass
1 week			Pass
Storage at 5 ± 3°C:			
24 h	0.5 h IVR time point		Pass
72 h			Fail[a]
1 week			Pass
24 h	24 h IVR time point		Pass
72 h			Pass
1 week			Pass
24 h	96 h IVR time point		Pass
72 h			Pass
1 week			Pass
(b) (4)			

Reviewer Comments:

1. The provided information supports the approval of proposed IVR method.
2. The evaluation by the Division of Pharmaceutical Analysis (DPA) found the IVR method acceptable for quality control and regulatory purposes.
3. DPA noted that the analytical method determines "**vincristine sulfate**" and not vincristine. Therefore, the name of the analyte should be changed to vincristine sulfate. The comments were conveyed to the Applicant.

➔ **The human factor study**

Since the formulation will be constituted in the hospital pharmacy, per the Agency's request, the Applicant conducted a human factor study to justify the preparation of the formulation with different pharmacists, different constitution temperatures and times, and different matrix parameters. The results are shown below.

Figure 6 **Field Test Data - In-Vitro Release Profiles**

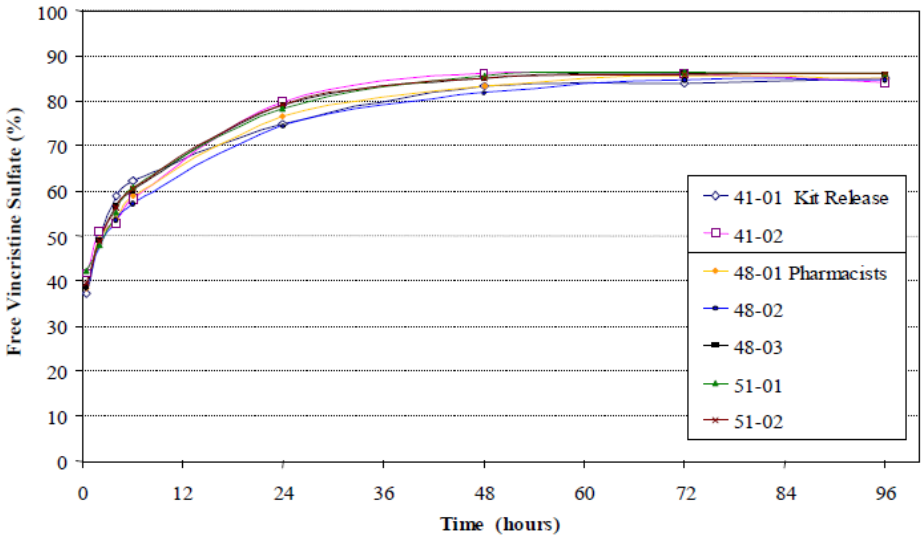
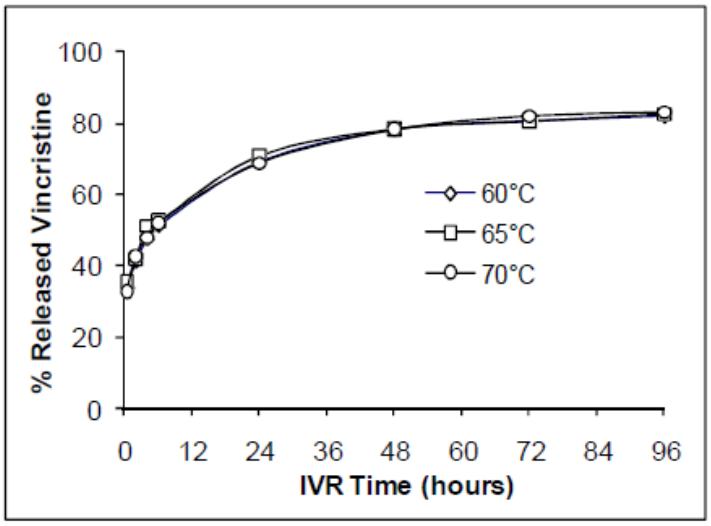


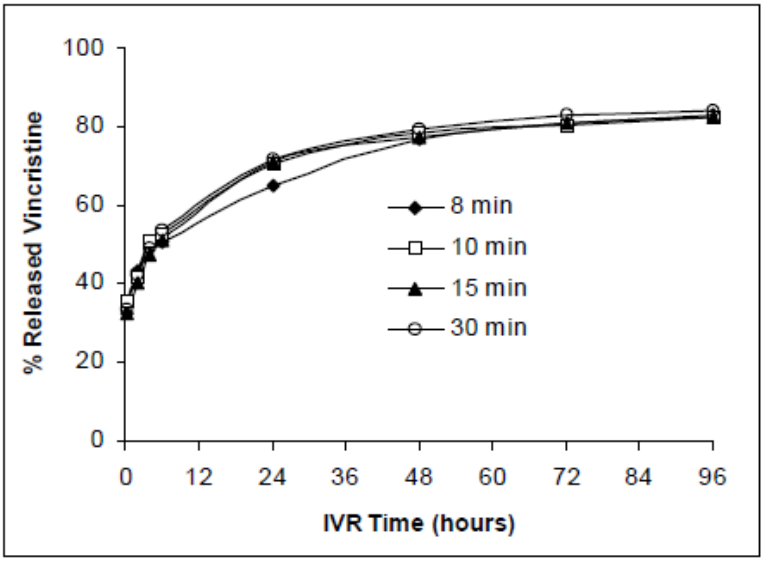
Figure 8 **Influence of VSLI Constitution Temperature on In Vitro Release of Vincristine**



Run QCR-0024.

Abbreviations: IVR = in vitro release; VSLI = Vincristine Sulfate Liposomes Injection.

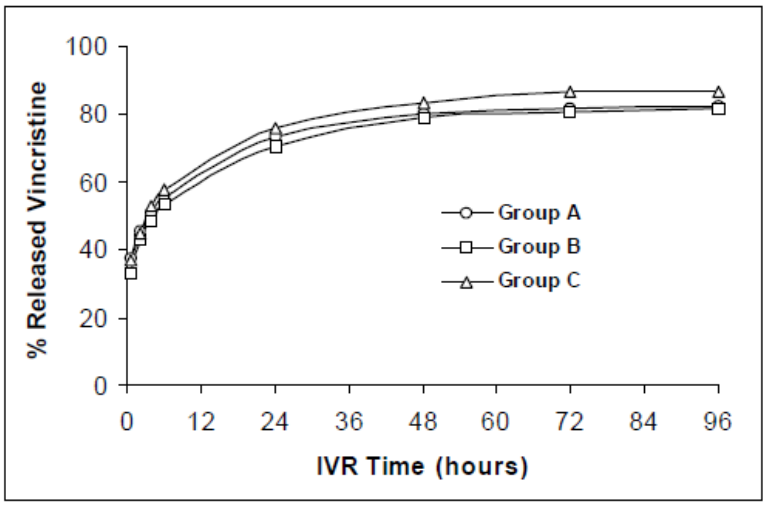
Figure 10 **Influence of Constitution Time at 65°C on In Vitro Release of Vincristine**



Run QCR-0024.

Abbreviation: IVR = in vitro release.

Figure 11 **In Vitro Release of VSLI Constituted at Matrix Parameters**



Run QCR-0024.

Abbreviations: IVR = in vitro release; VSLI = Vincristine Sulfate Liposomes Injection (0.16 mg/mL).

Reviewer Comment:

The results from the human factor study showed that constitution by different pharmacists and different constitution times and temperatures do not affect the release of vincristine sulfate.

APPENDIX 2.

In Vitro Release Method and Acceptance Criteria

➔ **In vitro Release Method**

Based on the evaluation of the information provided in the method development report and the Division of Pharmaceutical Analysis recommendation, the proposed IVR method is acceptable. The testing conditions are as follows;

Apparatus:	Shaker-waterbath
Media:	1-Butanol in PBS 2.75%
Volume:	105 mL
Pre incubation time:	1 h
Agitation speed:	70 rpm
Temperature:	37±0.1 °C

Conditions for HPLC Analysis

Column:	Waters Symmetry C8 column, 5 µm, 4.6 x 250 mm
Guard Column:	Waters Symmetry C8
Column temperature:	35°C
Detector:	UV at 297 nm

Autosampler tray temperature: 20ºC or ambient

Injection Volume:	40 µL
Flow Rate:	1.0 mL/min

Flow rate in between incubation time points longer than 6 hours: 0.1 mL/min

Isocratic condition:	pre-mixed mobile phase comprised of 30% mobile phase component A and 70% of mobi1e phase

➔ **In Vitro Release Acceptance Criteria**

The proposed acceptance criteria for the in vitro release assay are as follow:

In Vitro Release	Acceptance Criteria
0.5 hours	(b) (4)
6 hours	
24 hours	
72 hours	

During the review of this NDA submission the following three issues were identified, and the last 2 were sent to the Applicant in an information request letter dated 9/23/2011.

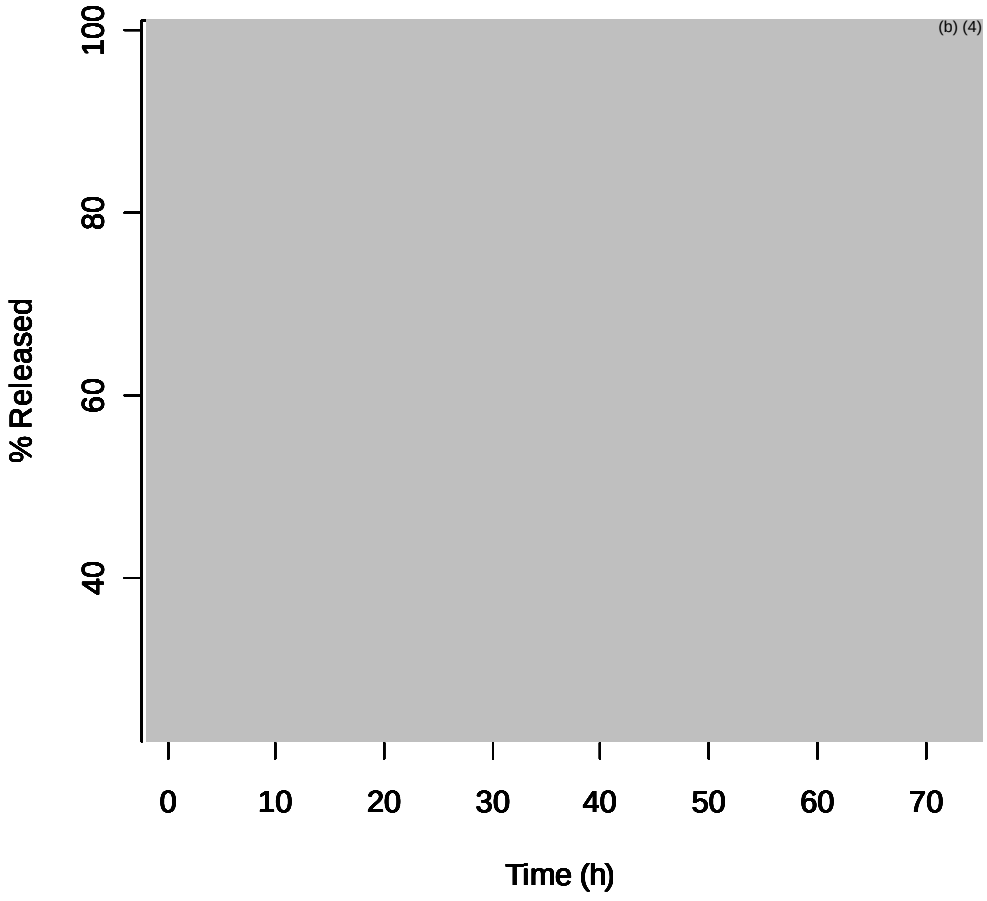
1. An FDA field laboratory validation request is recommended regarding the usage of 1-Butonol as in vitro release medium and its bio-relevance and discriminating ability.
2. In general, the in vitro release assay is conducted using at least 6 units for each lot. However in this NDA submission, only the value of a single unit/lot at each time

point is being reported. The Applicant should explain/justify why only one unit/lot was used for this assay.

3. The proposed acceptance criteria for the IVR assay are permissive with (b) (4) range at the first three time points and less than (b) (4) for the last time point. Based on the available data that were submitted, the following acceptance criteria for the IVR assay are recommended.

In Vitro Release	Acceptance Criteria
0.5 hours	(b) (4)
6 hours	
24 hours	
72 hours	

The following figures show the analyses conducted by the reviewer using the available data submitted in the NDA, to support the recommended acceptance criteria for the IVR assay. The following figure shows the dissolution profiles for the available 15 sets of data.



Based on these data, the recommended acceptance criteria for the release assay at 0.5 h, 6 h, 24 h and 72 h are shown in the following figures.

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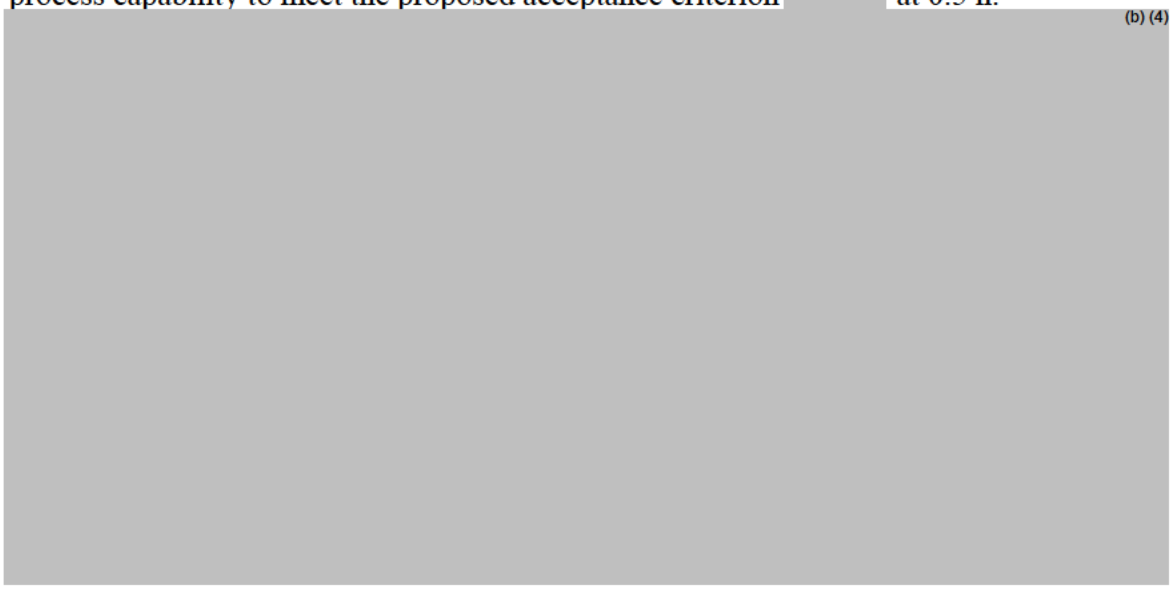
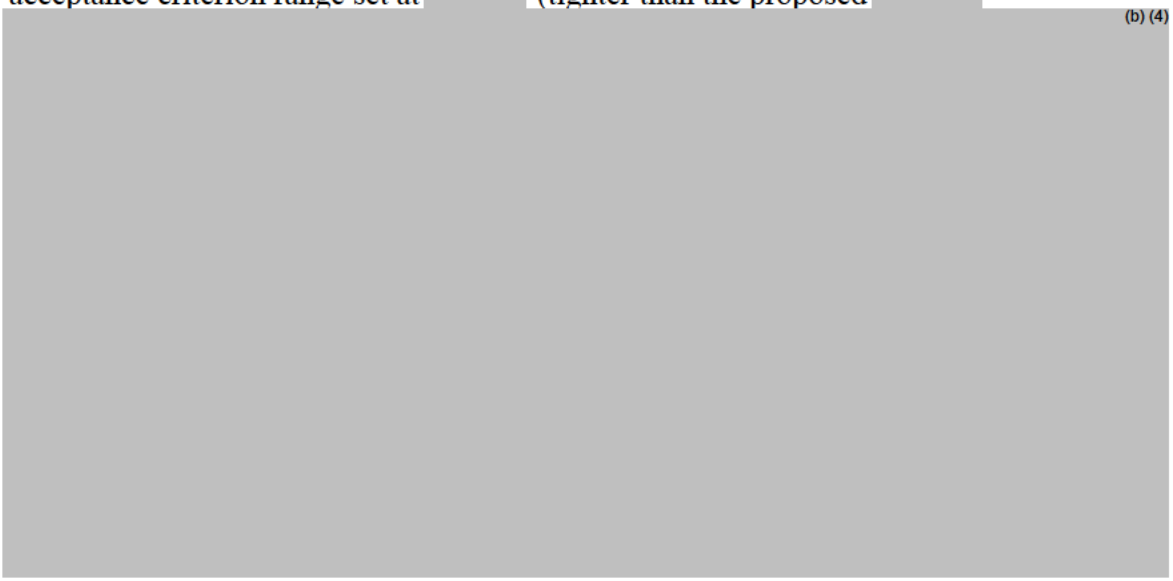
In Vitro Release	Acceptance Criteria
0.5 hours	(b) (4)
6 hours	
24 hours	
96 hours	

With the information provided, this Reviewer conducted process capability analyses with the consideration of stability data. The following figures show the results for the data at 0.5 h. The left panel shows the distribution of the release and the right panel indicates the process capability to meet the proposed acceptance criterion (b) (4) at 0.5 h.



The following figures show the similar charts for the in vitro release at 6 hours with the acceptance criterion range set at (b) (4) (tighter than the proposed (b) (4)



The following figures show the in vitro release at 24 hours with the acceptance criterion range set at (b) (4) tighter than the proposed (b) (4)

In addition, the Applicant proposed to change the last time point from 72 h to 96 h. The charts for 96 h are shown below.

Reviewer Comment:

Based on the above analyses, the following acceptance criteria using the proposed IVR method are recommended. The differences from the Applicant's proposed values are highlighted. In a submission dated 4/10/12 (SN # 0012), the Applicant accepted FDA's recommendation and updated the specifications table for the drug product and throughout the application accordingly.

In Vitro Release Acceptance Criteria for Marqibo Liposomes Injection	
Time	% Vincristine Sulfate Released
0.5 hours	(b) (4)
6 hours	
24 hours	
96 hours	

APPENDIX 3.

Validation Report

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION REPORT SUMMARY

TO: Xiao Hong Chen, CMC Reviewer
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: xiao.chen@fda.hhs.gov
Phone: (301)- (301) 796-1337
Fax: (301)- (301) 796-9850

FROM: FDA
Division of Pharmaceutical Analysis
James Allgire, Team Leader
Suite 1002
1114 Market Street
St. Louis, MO 63101
Phone: (314) 539-3813

Through: Benjamin J. Westenberger, Deputy Director
Phone: (314) 539-3869

SUBJECT: Methods Validation Report Summary

Application Number: 202497

Name of Product: MARQIBO® (vincristine sulfate liposomes injection) (0.16 mg/mL)

Applicant's Contact Person: Thomas Tarlow, VP, Regulatory Affairs and Quality Assurance

Address: 2207 Bridgepointe Parkway, Suite 250, San Mateo, CA 94404
Telephone: (650) 228-5066 Fax: (650) 228-5066

Date Methods Validation Consult Request Form Received by DPA: 9/19/2011

Date Methods Validation Package Received by DPA: 9/19/2011

Date Samples Received by DPA: 10/18/2011 and 11/02/2011

Date Analytical Completed by DPA: 2/29/2012

Laboratory Classification: **1.** Methods are acceptable for control and regulatory purposes. ☐
2. Methods are acceptable with modifications (as stated in accompanying report). ☒
3. Methods are unacceptable for regulatory purposes. ☐

Comments:

Cover memo and results attached.

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis
St. Louis, MO 63101
Tel. (314) 539-3815

Date: February 28, 2012

To: John Duan, Ph.D., Review Chemist (HFD-800)

Through: B. J. Westenberger, Deputy Director, Division of Pharmaceutical Analysis, (HFD-920)

From: Michael Trehy, Chemist (HFD-920)

Subject: Method Validation for NDA 202497
MARQIBO® (vincristine sulfate liposomes injection) (0.16 mg/mL)

The Division of Pharmaceutical Analysis (DPA) has evaluated the following method and found the method to be acceptable for quality control and regulatory purposes with the modifications listed below.

"NT 100-1552 In Vitro Release Determination of Vincristine from Vincristine Sulfate Liposomes Injection, 0.16mg/mL (VSLI)"

DPA has the following comments regarding the method.

1. The method needs to give each equation used and define each term used in the equation. The equations for calculating the vincristine sulfate concentrations are not given. The method also needs to specify which standard chromatograms, the initial calibration standards chromatograms or the daily bracketing SSS chromatograms, are to be used to calculate the concentration. The method only states the vincristine sulfate concentration is calculated using a validated EXCEL spreadsheet.

2. The method specifies preparation of a calibration standard but does not clearly indicate how to use this standard. Suggest adding a statement describing how to apply this standard to the evaluation of the system suitability standard.

3. The equations to calculate the "% Recovery from the theoretical concentration for each pre-run SSS injection" need to be given.

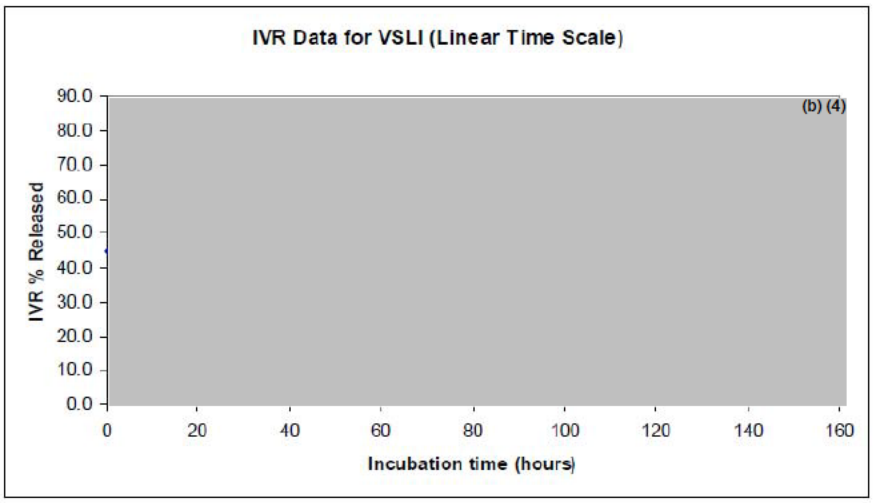
4. Table 1 should indicate which SSS injections are the pre-run SSS injections.

5. The methods title is"…determination of Vincristine from…" but the method always determines the Vincristine Sulfate concentration. So as not to mislead anyone the name should be changed to Vincristine Sulfate.

NT 100-1552 In Vitro Release Determination of Vincristine from Vincristine Sulfate Liposomes Injection, 0.16mg/mL (VSLI)

Results:

Time	Vincristine released	limit
0.5	(b) (4)	(b) (4)
2		
4		
6		
24		
48		
72		
96		
145		



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/s/

MICHAEL L TREHY
03/05/2012

BENJAMIN J WESTENBERGER
03/05/2012

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/s/

JOHN Z DUAN
04/11/2012

ANGELICA DORANTES
04/11/2012

Clinical Pharmacology Review

NDA	202-497/SDN1
Submission Date:	07 June 2011
Brand Name:	Marqibo®
Generic Name:	Vincristine Sulfate Liposomes Injection, VSLP
Formulation:	Liposomal Solution, Injection
OCP Reviewers:	Bahru A Habtemariam, Pharm.D.
OCP Team Leader:	Julie Bullock, Pharm.D.
OCP Division:	Division of Clinical Pharmacology V
ORM Division:	Division of Drug Oncology Products
Sponsor:	Talon Therapeutics Inc
Submission Type; Code:	Original/000; SE2
Dosing regimen:	2.25 mg/m^2 intravenously over 60 minutes every 7 days
Indications	Philadelphia Chromosome-negative (Ph-) Adult Acute Lymphoblastic Leukemia (ALL) patients in second or greater relapse or whose disease has progressed following two or more anti-leukemia therapies

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EXECUTIVE SUMMARY

The NDA for Marqibo® (Vincristine Sulfate Liposomes Injection, VSLI) was previously submitted under a separate NDA (#21-600) on 3/12/2004 for a Non-Hodgkin lymphoma (NHL) indication. On 1/14/2005, FDA issued a non-approval letter due to incomplete clinical data and problems with manufacturing facilities. The clinical pharmacology aspects of VSLI were found acceptable at the time of the previous submission.

In the current submission, the sponsor submitted results of a phase 2 study (N=60), following treatment with 2.25 mg/m^2 VSLI given on days 1, 8, 15, and 22 of a 28-day treatment cycle, to seek approval for treatment of acute lymphoblastic leukemia (ALL). The primary endpoint was overall remission (ORR), which was achieved by 20% of the patients.

Safety information was available from 101 patients following treatment with VSLI doses of 1.2 to 2.4 mg/m^2 in phase 1 and phase 2 studies. The rate of Grade 3 or more adverse events was 97% and the rate of serious adverse events was 78%. Among patients that were treated with the proposed dose of 2.25 mg/m^2, the most frequent adverse events were febrile neutropenia, neutropenia, anemia, thrombocytopenia, pyrexia, and peripheral neuropathy.

Pharmacokinetic data were available from seven patients with moderate (n=6) and severe (n=1) hepatic impairment, which were compared to the PK of patients with normal hepatic function who took part in a separate study. The Cmax and AUC of patients with moderate hepatic impairment were similar to those with normal hepatic function that took part in the pivotal study.

1.1 RECOMMENDATIONS

The proposed NDA is acceptable from clinical pharmacology perspective.

1.2 LABELING RECOMMENDATIONS

Please refer to Section 3 - Detailed Labeling Recommendations

Reviewer: Bahru A. Habtemariam, Pharm.D.
Division of Clinical Pharmacology 5

Team Leader: Julie Bullock, Pharm.D.
Division of Clinical Pharmacology 5

Cc: DDOP: CSO - **C Cottrell;** MTL - **E Kaminskas**; MO - **E Kaminskas**
DCP-5: Reviewers - **B Habtemariam**, TL - **J Bullock**,
DDD - **B Booth;** DD - **A Rahman**

1.3 CLINICAL PHARMACOLOGY SUMMARY

A separate NDA (21-600) application for Marqibo® was previously submitted for a NHL indication in March of 2004. Following review of NDA 21-600, the FDA issued a non-approval letter on January 14, 2005. The main reason for non-approval was that the clinical data were deemed insufficient to support approval for the proposed indication. In addition, NDA 21-600 had manufacturing issues the sponsor needed to address.

In the present submission, the sponsor is seeking approval for ALL under a new NDA number (202-497). To support the ALL indication, the sponsor submitted results of a single arm, phase 2 study (N=65) in patients with ALL that were treated with VSLI doses of 2.25 mg/m^2. The primary endpoint for the pivotal study was overall response rate (ORR). Study results show that 20% of patients achieved the primary endpoint of ORR.

Safety data were available from 101 patients that took part in the phase 1 dose escalation trial and the pivotal phase 2 trial that were treated with VSLI doses of 1.2 to 2.4 mg/m^2. The rate of Grade 3 or more adverse events was 97% and the rate of serious adverse events was 78%. Among patients that were treated with the proposed dose of 2.25 mg/m^2 most frequent adverse events were febrile neutropenia, neutropenia, anemia, thrombocytopenia, pyrexia, and peripheral neuropathy.

Pharmacokinetic data were available from 13 patients that took part in the pivotal study. Because PK data were available from a very small subset of patients that took part in the pivotal study, exposure-response analysis for safety and effectiveness could not be conducted.

The sponsor also submitted PK data from seven subjects with moderate (n=6) and severe (n=1) hepatic impairment. The Cmax and AUC of patients with moderate hepatic impairment was similar to the Cmax and AUC of patients that took part in the pivotal study, who had otherwise normal hepatic function.

2 QUESTION BASED REVIEW

Marqibo® (Vincristine Sulfate Liposomes Injection, VSLI) has been reviewed previously under NDA 21-600, which was submitted on 3/12/2004 for NHL indication. For brevity, only QBR questions regarding this current NDA submission will be addressed below. For additional information please see posted clinical pharmacology review under NDA 21-600 in DARRTs (G Williams, 1/4/05). The original NDA for VSLI was not approved due to insufficient clinical data and manufacturing issues; non-approval letter was issued on 1/14/2005.

2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

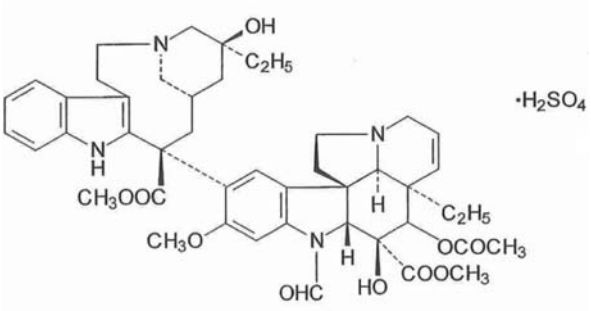
Physico-chemical properties

The Marqibo® Kit for the Preparation of Vincristine Sulfate Liposomes Injection is composed of

- Vincristine sulfate, USP (5 mg/5 mL) (VSI)
- Sphingomyelin/cholesterol liposomes injection (103 mg/mL, 1 mL) (SCLI)
- Sodium phosphate injection (14.2 mg/mL, 25 mL) (SPI) Sodium phosphate injection (14.2 mg/mL, 25 mL) (SPI)

The three component vials are packaged in a single Marqibo® Kit. The Marqibo® (vincristine sulfate liposome injection, 0.16 mg/mL) is compounded in accordance with the Package Insert Label at the dispensing pharmacy. Vincristine sulfate is a vinca alkaloid isolated from the periwinkle plant (Vinca rosea Linn.). The structural formula of Vincristine Sulfate is presented below:

- Structural formula:



Molecular Formula: $C_{46}H_{56}N_4O_{10} \cdot H_2SO_4$
Molecular Weight: 923.04

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

The active ingredient in Marqibo® is vincristine sulfate. Vincristine binds to tubulin, altering the tubulin polymerization equilibrium, resulting in altered microtubule structure and function. At low concentrations, vincristine stabilizes the spindle apparatus, preventing chromosome segregation, triggering metaphase arrest and inhibition of mitosis. Low vincristine

concentrations over a short duration results in metaphase arrest followed by abnormal cell cycle progression and potentially sublethal, but antiproliferative, effects. At higher concentrations, disruption and total depolymerization of microtubules are observed. Vincristine-induced mitotic arrest is reversible; cells proceed through the growth cycle if the drug is removed. In contrast, long term exposure and high concentrations result in lethal cytotoxicity.
Marqibo® is a novel sphingomyelin/cholesterol liposomal encapsulated formulation of vincristine (VCR). The rationale for liposomal encapsulation of VCR is based on the potential for these nanoparticle carriers to increase the circulation time of the drug and to increase the amount of drug that penetrates and accumulates at the tumor site, thus enhancing cytotoxic effect at the G2/M phase of the cell cycle. Nonclinical models have demonstrated that encapsulation of VCR in liposomes provides increased anticancer efficacy with toxicities comparable to standard vincristine.

2.1.3 What are the proposed dosage and route of administration?

The proposed dose of Marqibo® is 2.25 mg/m^2 intravenously over 60 minutes every 7 days.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

To support the ALL indication in the current submission, the sponsor submitted results from three clinical and clinical pharmacology studies (

Table 1):

- Study VSLI-06 was a dose escalation study in ALL patients that was used to select dose for the pivotal phase 2 study (HBS407).
- Study HBS407 was a phase two efficacy study in Philadelphia chromosome negative (Ph-) ALL patients.
- Study VSLI-12-EPHARM was clinical pharmacology where the PK of single dose VSLI was evaluated in patients with hepatic impairment.

Table 1. Summary of clinical and clinical pharmacology studies submitted with the current NDA.

Study (N)	Primary Objective	Patient Population	Studied Doses	Major Findings
VSLI-06 (N=36)	To determine MTD	Relapsed/ refractory Ph-Adult ALL patients	1.5, 1.825, 2, 2.25, 2.4, 2.6 and 2.8 mg/m^2 given on days 1, 8, 15, and 22 of a 28-day treatment cycle	MTD determined to 2.25 mg/m^2
HBS407 (N=65)	To determine Rate of CR + CRi	Relapsed/ refractory Ph-Adult ALL patients	VSLI at 2.25 mg/m^2 IV over 1-hour on days 1, 8, 15, and 22 of a 28-day treatment cycle	20 % of patients achieved CR or CRi
VSLI-12-EPHARM (N=7)	To evaluate single dose PK in hepatic impairment patients	Malignant melanoma with hepatic impairment	1.0 mg/m^2 every 14 days	

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

In the pivotal phase 2 study, which is supporting the current NDA submission, the primary clinical endpoint was overall remission rate (complete and incomplete recovery).

Clinical response assessment is summarized in

Table 2. Following treatment with VSLI doses of 2.25 mg/m^2, a total of 11 subjects (20.8%; 95% CI: 10.8, 34.1) achieved CR+CRi based on IRRC determination in the IRRC Evaluable Population, 13 subjects (20.0%; 95% CI: 11.1, 31.8) based on PI determination in the ITT Population, and 11 subjects (16.9%; 95% CI: 8.8, 28.3) based on IRRC determination in the ITT Population.

Table 2. Summary of efficacy assessment of ALL patients in study HBS407.

Best Response Assessment	VSLI		
	IRRC (IRRC Evaluable Population) (N = 53)	**IRRC (ITT Population) (N = 65)**	**PI (ITT Population) (N = 65)**
Overall Remission CR+CRi [n (%)]	11 (20.8)	11 (16.9)	13 (20.0)
Exact 95% CI[a] (Clopper-Pearson)	(10.8 - 34.1)	(8.8 - 28.3)	(11.1 - 31.8)
Complete Remission (CR) [n (%)]	8 (15.1)	8 (12.3)	7 (10.8)
Exact 95% CI[a] (Clopper-Pearson)	(6.7 - 27.6)	(5.5 - 22.8)	(4.4 - 20.9)
CR with Incomplete Blood Count Recovery (CRi) [n (%)]	3 (5.7)	3 (4.6)	6 (9.2)
Exact 95% CI[a] (Clopper-Pearson)	(1.2 - 15.7)	(1.0 - 12.9)	(3.5 - 19.0)

2.2.3 Exposure-response

There is not sufficient PK and efficacy data to conduct meaningful exposure-response analysis in the current submission. In the pivotal phase 2 study where efficacy data were collected, PK data were available only from 13 patients. The summary of the studies that provided PK, safety, or efficacy data in the current submission are provided below (**Table 3**).

Table 3. Studies and number of patients (N) with PK samples

Study (phase)	Dosing Schedule	N	Population	Study Objective
VSLI-12-EPHARM (1)	1 mg/m^2 q14d	7	MM/Hepatic	Single dose PK in Hepatic impairment
HBS407 (2)	2.25 mg/m^2 q7d	13	Ph- ALL	Efficacy

2.2.3.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

Following the proposed dose of 2.25 mg/m^2 (n=65) in the pivotal phase 2 study, the most

frequent grade 3 or more (grade 3+) adverse events were febrile neutropenia (30%), neutropenia (18%), anemia (17%), thrombocytopenia (17%), pyrexia (15%), and peripheral neuropathy (12%) (see **Table 4**). However, because adverse events were collected only for one dose level and PK samples were not collected, dose-response or exposure-response analyses could not be conducted.

Table 4. Summary of the highest frequency adverse events observed in study HBS407

Any Adverse Event	Grade 3-5 n (%)
Febrile Neutropenia	25 (30.1)
Neutropenia	15 (18.1)
Anemia	14 (16.9)
Thrombocytopenia	14 (16.9)
Pyrexia	12 (14.5)
Neuropathy Peripheral	10 (12.0)

2.2.3.2 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The dose for the pivotal study was selected based on a phase 1 dose escalation study using the traditional 3+3 study design. The dose was selected based on safety endpoints. PK data were not collected in the dose escalation trial, as such, exposure-response analysis was not used to aid dose selection. The pivotal phase 2 study also used VSLI dose of 2.25 mg/m^2 in all patients and PK data were collected in small number of patients, therefore exposure-response analysis was not performed to assess adequacy of the selected dose**.**

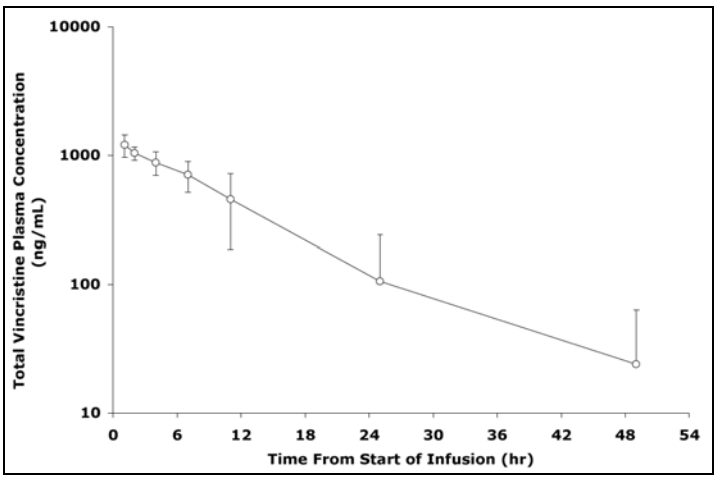
2.2.4 Pharmacokinetic characteristics of the drug and its major metabolites

The PK properties of VSLI have been characterized during the previous submission. In the present submission, the sponsor obtained single dose PK samples of VSLI in the pivotal study from 13 subjects (**Table 5**). In addition, the plasma concentration vs. time profile of VSLI shows the presence of detectable plasma concentration up to 48-hours post dose (**Figure 1**).

Table 5. Summary of the PK parameters of VSLI following single 2.25 mg/m^2 dose.

	C_{max} (ng/mL)	$AUC_{0\text{-last}}$ (ng•hr/mL)	$AUC_{0\text{-inf}}$ (ng•hr/mL)	$t_{1/2}$ (hr)	CL (mL/hr)
N	13	13	12	12	12
Mean	1220	13732	14566	7.66	345
CV%	18.8	41.3	43.7	41.5	51.2
Min	919	6975	7036	4.49	148
Median	1230	13502	13680	6.61	302
Max	1720	24036	26074	12.6	783

Figure 1. Mean plasma concentration-time profile of VSLI following single dose.



2.2.4.1 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Data from healthy volunteers were not included in this submission.

2.2.4.2 Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?

Because PK data were not available from wide range of doses, reliable dose-proportionality assessment can not be made for VSLI.

2.2.4.3 How do the PK parameters change with time following chronic dosing?

VSLI appears to follow time-invariant PK. During the previous NDA submission, the AUCs of total vincristine were compared for cycle 1 and cycle 3. In both cycles, VSLI dose of 2 mg/m^2 was administered. The AUCs of total vincristine were similar for cycles 1 and 3, suggesting little accumulation takes place during the cycle.

2.2.4.4 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

VSLI pharmacokinetic parameters were highly variable. Unexplained inter-individual variabilities were 41 and 51% for AUC and clearance parameter, respectively (**Table 5)**.

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Influence on Exposure

In the present submission, the sponsor submitted results of PK study in patients with hepatic impairment (N=7). Six of the seven subjects had Child Pugh scores 7-8, which is consistent with a moderate hepatic impairment per FDA's guidance. One of the six subjects had a Child-Pugh

Score of 11, which is consistent with severe hepatic impairment per FDA's guidance. In addition, enrolled patients have bilirubin levels of 1.6 to 3 mg/dL. However, since the sponsor did not provide the normal reference range for the bilirubin values in this study, we can not determine the liver function category according to NCI Organ Dysfunction Working Group criteria. **Table 6** below summarizes the PK of patients with moderate hepatic impairment. The one patient with severe hepatic impairment had similar Cmax and AUC values as those with moderate impairment.

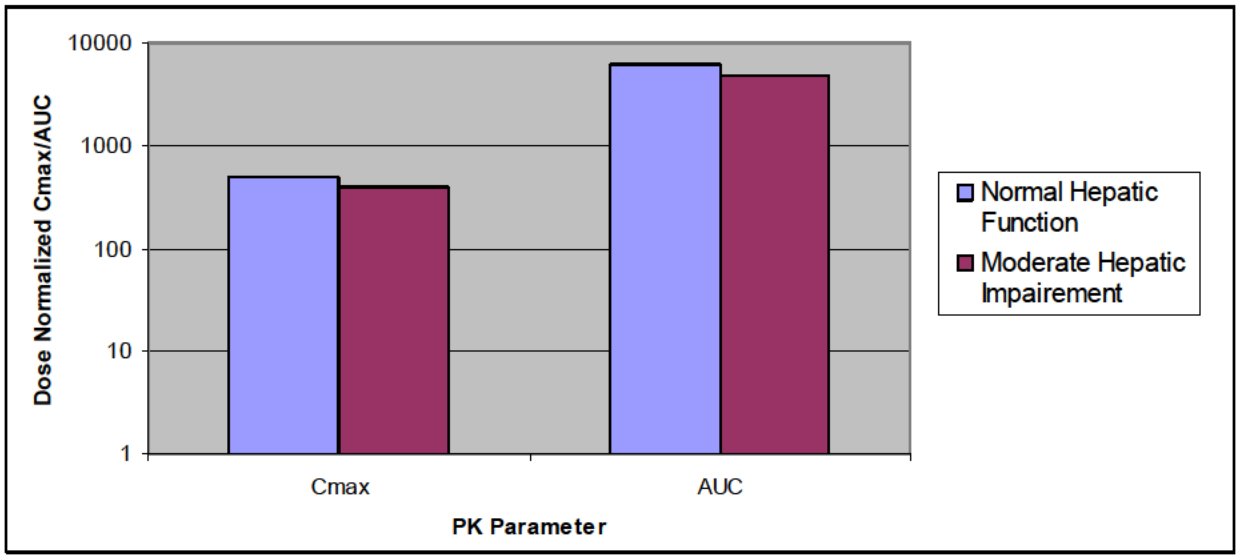
Table 6. Summary of PK of VSLI in patients with moderate hepatic function

	Cmax (ng/mL)	AUC(0-tlast) (ng*hr/mL)	AUC(0-∞) (ng*hr/mL)	Half-life (hr)	CL (L/hr)
N	6	6	6	4	4
Mean	389	4796	6252	9.9	392
Median	399	4926	5358	10.1	385
min	217	1720	4650	8.3	199
max	531	9607	9640	11.2	600
%CV	31	59	37	14.1	42

PK comparison:

Comparison of mean Cmax and AUC values between subjects with normal hepatic function that participated in study HBS407 and patients with moderate hepatic impairment that took part in study VSLI-12-EPHARM show that moderate hepatic impairment does not influence the PK of VSLI (**Figure 2**). In addition, clearance and half-life comparisons between subject with normal hepatic function and those with moderate hepatic impairment show generally similar values (**Table 5** and **Table 6**).

Figure 2. Mean Cmax and AUC values of patients with normal function (study HBS407) and patients with moderate hepatic function (Study VSLI-12-EPHARM).



2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Renal impairment

The influence of renal impairment on the PK of VSLI was not characterized in the previous or present submission. However, an ADME data submitted in the previous NDA submission showed urinary excretion was a minor excretion route of vincristine, with less than 8% of the injected dose eliminated by the renal route over 96 hours. Therefore, renal impairment is unlikely to influence the PK of VSLI.

2.3.2.2 Hepatic Impairment

Moderate hepatic impairment does not influence the PK of VSLI, therefore no dose adjustment is recommended for patients with mild and moderate hepatic impairment. The sponsor did not study the influence of severe hepatic impairment on the PK of VSLI; therefore a specific dose adjustment recommendation can not be make for patients with severe hepatic impairment.

2.4 EXTRINSIC FACTORS

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

No specific studies or analyses were designed to evaluate the effects of factors such as herbal products, diet, smoking or alcohol use on the PK or PD of VSLI.

2.4.2 Drug-drug interactions

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

See previous NDA review.

No studies of the metabolism of VSLI have been performed, but a literature review of the metabolism of vincristine was carried out by the sponsor. Evidence from both in vitro and in vivo studies supports the involvement of the cytochrome P4503A subfamily of enzymes in the metabolism of vincristine. In vitro competitive inhibition studies with human liver microsomes suggest that CYP3A4 is involved in vincristine metabolism. Li et al. have suggested that human CYP2C19 and CYP2D6 may also be involved. A competitive inhibition study with paclitaxel and docetaxel supports the involvement of the CYP2C subfamily in the metabolism of vincristine.

Studies in humans and animals suggest that metabolism and/or biodegradation of vincristine yields multiple (6 to 11) peaks. However, only a few of these peaks have been identified: (b) (4) [redacted] The structures and identities of many of the metabolites or degradation products and the pathways through which they are formed remain largely unknown.

No studies have been conducted in either animals or humans to determine the metabolism of the lipid components of VSLI. Both sphingomyelin and cholesterol are constituents of normal body tissues and the Applicant assumes that injected sphingomyelin and cholesterol enter the normal metabolic pathways for these lipids.

2.5 ANALYTICAL SECTION

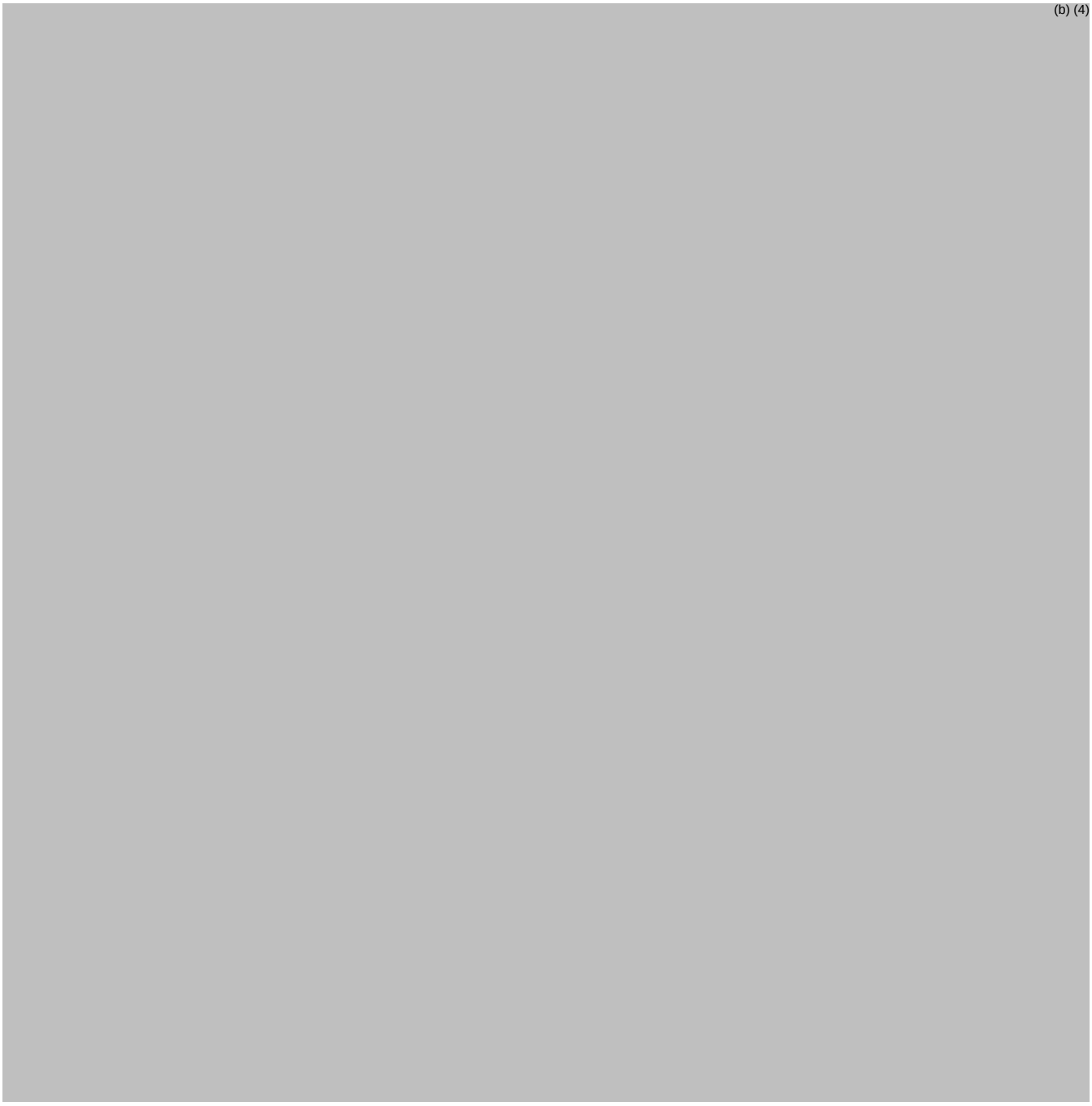
2.5.1 Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

Analytical procedures used to characterize the free or total concentrations of VSLI were assessed in the previous NDA submission, which were the same ones used for the present NDA.

3 DETAILED LABELING RECOMMENDATIONS

3.1 PROPOSED LABELING

(b) (4)



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

/s/

BAHRU A HABTEMARIAM
03/22/2012

JULIE M BULLOCK
03/23/2012

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

NDA 202497 is a 505(b)(2) application where the sponsor (Talon) is referencing its own previously submitted, unapproved, NDA (21-600) and data on the traditional vincristine sulfate.

	Information		Information
NDA/BLA Number	202497	**Brand Name**	Marqibo
OCP Division (I, II, III, IV, V)	5	**Generic Name**	Vincristine Sulfate Liposomes Injection
Medical Division	Oncology	**Drug Class**	Hematology
OCP Reviewer	Bahru A Habtemariam, Pharm.D	**Indication(s)**	For the treatment of adult Philadelphia chromosome negative (Ph-) acute lymphoblastic leukemia (ALL) in second or greater relapse or in patients whose disease has progressed following two or more anti-leukemia therapies
OCP Team Leader	Julie Bullock, Pharm.D	**Dosage Form**	solution
Pharmacometrics Reviewer	NA	**Dosing Regimen**	2.25 mg/m^2 as an intravenous (IV) infusion over 1 hour (±10 minutes) every 7 days on Days 1, 8, 15, 22 of a 28-day treatment cycle
Date of Submission	July 12, 2011	**Route of Administration**	Intravenous
Estimated Due Date of OCP Review	April 1, 2012	**Sponsor**	Talon
Medical Division Due Date	April 15, 2012	**Priority Classification**	Standard
PDUFA Due Date	May 12, 2012		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X	17	**17**	The sponsor submitted a total of 17 studies including one pivotal phase 2 study and 1 dose escalation phase 1 studies. Most of the studies are phase one study. Some of the studies are from the previous NDA.
Tabular Listing of All Human Studies	**X**	**17**	**17**	
HPK Summary				
Labeling	**X**			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	**X**	**8**	**8**	
Healthy Volunteers-				
single dose:				
multiple dose:				

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:	**X**	**1**	**1**	This is a very small study (n=7) of which 6 and 1 patients had Child Pugh classification classes B and C, respectively
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:		**2**	**2**	
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	**X**	**512**	**-**	
Total Number of Studies	**2**	**17**	**17**	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			X	
5	Has a rationale for dose selection been submitted?			X	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?			X	
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	X			
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		X		
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		X		
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?		X		
19	Was the translation (of study reports or other study information) from				

	another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Bahru A. Habtemariam, Pharm.D.	September 1, 2011
Reviewing Clinical Pharmacologist	Date
Julie Bullock, Pharm.D.	September 1, 2011
Team Leader/Supervisor	Date

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

/s/

BAHRU A HABTEMARIAM
09/09/2011

JULIE M BULLOCK
09/16/2011

ONDQA BIOPHARMACEUTICS FILLING REVIEW

NDA#:	**202-497**
Submission Date:	07/12/2011
Brand Name:	Marqibo
Generic Name:	Vincristine Liposomal Injection
Formulation:	Injection
Strength:	0.16 mg/mL
Applicant:	Talon Therapeutics
Reviewer:	John Duan, Ph.D.
Submission Type:	Original NDA

The applicant is submitting a New Drug Application pursuant to Section 505 (b)(2) of the Federal Food, Drug, and Cosmetics Act for Marqibo (Vincristine Sulfate Liposomes Injection) to seek the accelerated registration of Marqibo as the single agent treatment for the indication of "the treatment of adult Philadelphia chromosome negative (Ph-) acute lymphoblastic leukemia (ALL) in second or greater relapse or in patients whose disease has progressed following two or more anti-leukemia therapies."

REVIEWER COMMENTS

1. An FDA field laboratory validation request is recommended, regarding the usage of 1-Butonol as in vitro release medium and its bio-relevance and discriminating ability.
2. At lease 6 units for each lot should be used for the in vitro release assay. However in this submission, only a single value is available for each lot at each time point for the IVR assay. Please clarify.
3. The proposed acceptance criteria for the IVR assay are permissive. Therefore, we recommend the following acceptance criteria, which are based on the limited data provided in the submission. If you have a different proposal, please submit supporting data, including the individual value with at least 6 units at each time point, the mean, the standard deviation and the plots.

In Vitro Release	Acceptance Criteria
0.5 hours	(b) (4)
6 hours	
24 hours	
72 hours	

RECOMMENDATION

There are no filing issues from the Biopharmaceutics perspective. Comment 1 should be conveyed to the CMC Lead and Comment 2 to 3 should be conveyed to the Applicant.

_____ _____

John Duan, Ph.D. Date
Reviewer
ONDQA Biopharmaceutics

_____ _____

Angelica Dorantes, Ph.D. Date
ONDQA Biopharmaceutics Team Leader

cc: NDA 202497
Patrick Marroum, John Duan

APPENDIX. The Biopharmaceutics related information

The Marqibo Kit is for the treatment of Philadelphia chromosome-negative (Ph-) acute lymphoblastic leukemia (ALL) in adults in second relapse or whose disease has progressed after 2 or more treatment lines of antileukemia therapy. The clinical dose of VSLI is 2.25 mg/m^2, administered weekly as a 1-hour IV infusion.

1. The composition of the drug product

The Marqibo Kit for the Preparation of Vincristine Sulfate Liposomes Injection (Marqibo Kit) is a kit containing 3 drug product components from which Vincristine Sulfate Liposomes Injection (0.16 mg/mL) (VSLI) is constituted. VSLI is a liposomal formulation of vincristine and its composition is provided in the following table.

Source	Component	Quality Standard	Function of Source Component	Quantity per mL VSLI (mg/mL)	Quantity per vial VSLI (mg/vial)
VSI (Section 3.2.P.1 [Vincristine Sulfate Injection, Hospira])	Vincristine sulfate[a]	USP	Active ingredient	0.16	5.0
	Mannitol	USP	(b) (4)	16.1	500.0
					(b) (4)
SCLI (Section 3.2.P.1 [Sphingomyelin/ Cholesterol Liposomes Injection, Cangene])	Sphingomyelin	Internal DMF (b) (4)	Functional liposome excipient	2.37	73.5
	Cholesterol HP	NF DMF (b) (4)	Functional liposome excipient	0.95	29.5
	Citric acid, (b) (4)	USP	(b) (4)	1.08	33.6
	Sodium citrate, (b) (4)	USP		1.14	35.4
	(b) (4) (ethanol)	USP			(b) (4)
SPI (Section 3.2.P.1 [Sodium Phosphate Injection, Jubilant HollisterStier])	Dibasic sodium phosphate, (b) (4)	USP		11.45[c]	355.0[c]
	Sodium chloride	USP		7.26	225.0
VSI, SCLI, SPI					(b) (4)
			VSLI total volume	1 mL	31 mL

Abbreviations: AR = as required; DMF = Drug Master File; HP = High Purity; NF = National Formulary; qs = quantity sufficient; USP = United Stated Pharmacopoeia; VSLI = Vincristine Sulfate Liposomes Injection (0.16 mg/mL).

[a] (b) (4)

[b] Letters of Authorization to the DMFs are provided in Section 1.4.1.

[c] (b) (4)

2. IVR Assay

In vitro release (IVR) assays are used for liposomal drug products to verify performance as part of product quality control (QC) testing. The proposed IVR conditions are as follows.

Apparatus:	Shaker-waterbath
Media:	1-Butanol in PBS 2.75%
Volume:	105 mL
Pre incubation time:	1 h
Agitation speed:	70 rpm
Temperature:	37±0.1 °C

Conditions for HFLC Analysis

Column:	Waters Symmetry C8 column, 5 µm, 4.6 x 250 mm
Guard Column:	Waters Symmetry C8
Column temperature:	35°C
Detector:	UV at 297 nm

Autosampler tray temperature: 20ºC or ambient

Injection Volume:	40 µL
Flow Rate:	1.0 mL/min

Flow rate in between incubation time points longer than 6 hours: 0.1 mL/min

Isocratic condition:	pre-mixed mobile phase comprised of 30% mobile phase component A and 70% of mobi1e phase

The proposed acceptance criteria for the in vitro release assay are as follows.

In Vitro Release	Acceptance Criteria
0.5 hours	(b) (4)
6 hours	
24 hours	
72 hours	

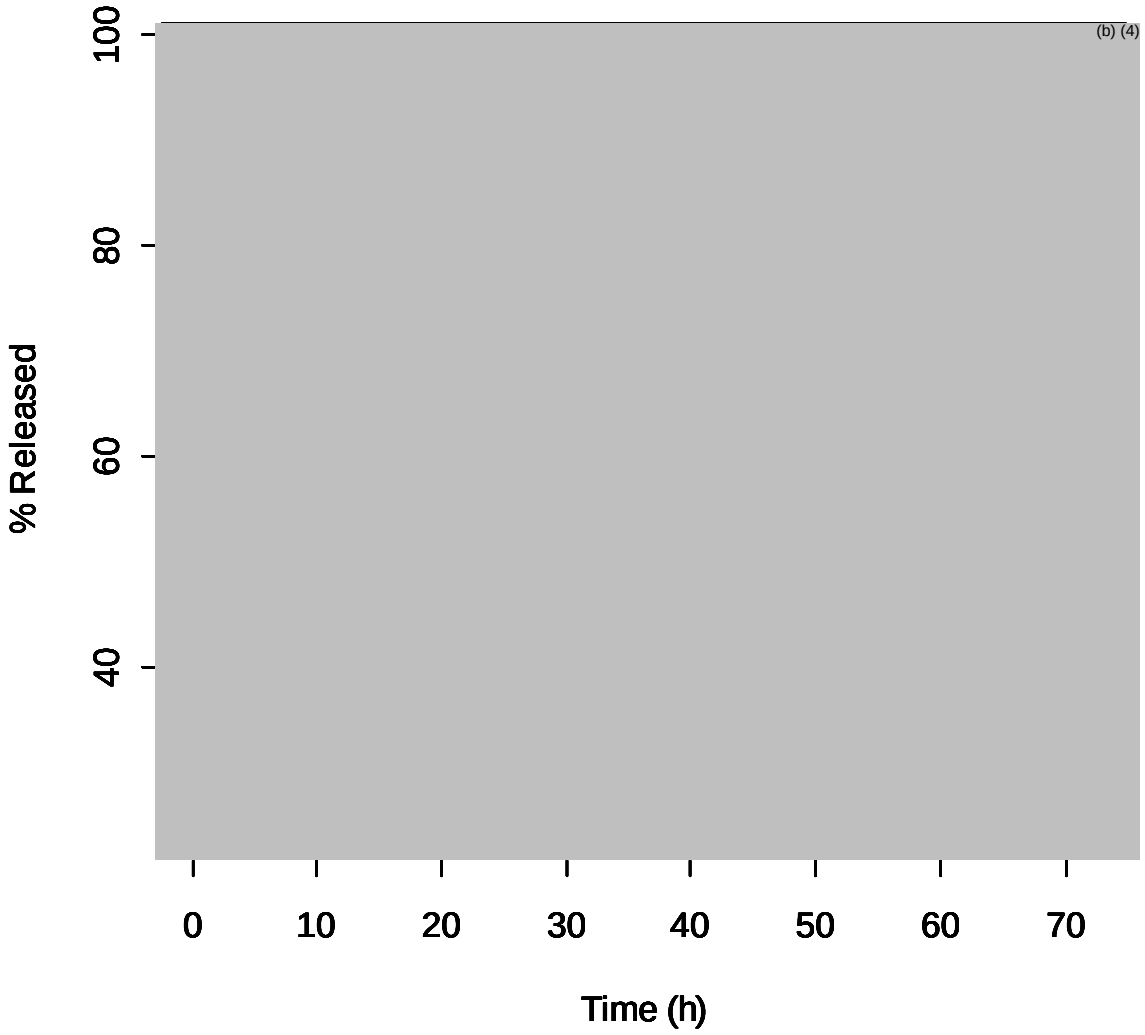
The following three issues were identified, although none of them is a filing issue.

1. An FDA field laboratory validation request is recommended regarding the usage of 1-Butonol as in vitro release medium and its bio-relevance and discriminating ability.
2. In general, the in vitro release assay is conducted using at least 6 units for each lot. However in this NDA submission, only the value of a single unit/lot at each time point is being reported. The Applicant should explain/justify why only one unit/lot was used for this assay.
3. The proposed acceptance criteria for the IVR assay are permissive with (b) (4) range at the first three time points and less than (b) (4) for the last time point. Based on the available data that were submitted, the following acceptance criteria for the IVR assay are recommended.

In Vitro Release	Acceptance Criteria
0.5 hours	(b) (4)
6 hours	
24 hours	
72 hours	

The following figures show the preliminary analyses that were conducted by this reviewer using the available data submitted in the NDA, to support the recommended acceptance criteria for the IVR assay.

The following figure shows the dissolution profiles for the available 15 sets of data.



Based on these data, the recommended acceptance criteria for the release assay at 0.5 h, 6 h, 24 h and 72 h are shown in the following figures.

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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.

/s/

JOHN Z DUAN
09/07/2011

ANGELICA DORANTES
09/07/2011