

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202497Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 202497

SUPPL #

HFD # 161

Trade Name Marqibo

Generic Name vinCRISTine sulfate LIPOSOME injection

Applicant Name Talon Therapeutics

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 14103

Oncovin

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

VSLI-06 Phase 1/2, multicenter, open-label, dose escalation study of VSLI combined with dexamethasone. AND

HBS407 Phase 2, international, multicenter, open-label, single-arm trial to evaluate the effect of Marqibo in adult patients with Ph- ALL or lymphoblastic lymphoma in second or greater relapse, or patients with Ph- ALL or lymphoblastic lymphoma whose disease progressed after 2 or greater treatment lines of anti-leukemia chemotherapy.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

VSLI-06 and HBS407

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # 059056 YES ! NO
! Explain:

Investigation #2
IND # 059056 YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

=====

Name of person completing form: Amy Baird
Title: Regulatory Project Manager
Date: August 9, 2012

Name of Office/Division Director signing form: Ann T. Farrell, MD
Title: Division Director, Division of Hematology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

AMY C BAIRD
08/09/2012

ANN T FARRELL
08/09/2012



June 23, 2011

Reference: NDA 202497: Marqibo® (vincristine sulfate liposomes injection)

Subject: Debarment Certification Statement

I, Thomas J. Tarlow, Vice President Regulatory Affairs and Quality Assurance, Talon Therapeutics (the "Applicant"), hereby certify that Talon Therapeutics did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

IN WITNESS WHEREOF, the undersigned has signed this certificate on behalf of Talon Therapeutics on the 23th day of June, 2011.

Talon Therapeutics INCORPORATION

by: 
Name: Thomas J. Tarlow
Title: Vice President, Regulatory Affairs and Quality Assurance

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # 202497 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Marqibo Established/Proper Name: vinCRIS^tine sulfate LIPOSOME injection Dosage Form: Injection		Applicant: Talon Therapeutics, Inc. Agent for Applicant (if applicable):
RPM: Amy Baird		Division: Division of Hematology Products
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Oncovin NDA 014103</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>API is the same in Oncovin and Marqibo. The only effect of liposome is to change the kinetics of vincristine by modifying e.g., slowing the release of vincristine from the liposome. The sponsor provided in-vitro and in-vivo data showing that vincristine is released from the liposome.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input checked="" type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR

The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<ul style="list-style-type: none"> Previous actions (<i>specify type and date for each action taken</i>) 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). 	<input type="checkbox"/> Received N/A
<ul style="list-style-type: none"> Application Characteristics³ <p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): NME</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input checked="" type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC </p> <p> NDAs: Subpart H <input checked="" type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </p> <p> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p> BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies </p> <p> REMS: <input checked="" type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required </p> <p>Comments:</p>	
<ul style="list-style-type: none"> BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter) 	<input type="checkbox"/> Yes, dates
<ul style="list-style-type: none"> BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>) 	<input type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Public communications (<i>approvals only</i>) <ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other – ASCO Burst

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLA: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

Copy of this Action Package Checklist ⁴	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Approval
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	8/7/2012
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	7/12/2011
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	NA

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	8/17/2012
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	7/12/2011
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	8/7/2012
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	Proprietary name review (acceptable) 12/15/2011
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA 7/26/2012 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) 7/31/2012 <input checked="" type="checkbox"/> ODPD (DDMAC) 7/31/2012; 6/15/2012 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews ,
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input type="checkbox"/> Not a (b)(2) 7/11/2012 <input type="checkbox"/> Not a (b)(2) 8/6/2012
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included 8/9/2012
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>N/A</u> If PeRC review not necessary, explain: <u>Orphan Designation Granted 1/15/2003 for Multiple Myeloma</u> • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before</i>) 	Pediatric page not reviewed by PeRC b/c orphan status. <input type="checkbox"/> Included

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

<i>finalized)</i>	
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>)	7/31/2012; 7/30/2012; 7/27/2012; 7/26/2012; 7/19/2012 (2); 6/28/2012; 6/12/2012; 6/8/2012; 5/23/2012; 5/18/2012; 5/3/2012; 4/25/2012; 4/18/2012; 4/17/2012; 4/11/2012; 4/5/2012 (2); 3/30/2012 (3); 3/28/2012; 3/26/2012; 3/22/2012; 3/15/2012 (2); 3/13/2012; 3/9/2012; 3/2/2012; 2/29/2012 (2); 2/22/2012; 2/9/2012; 2/6/2012 (2); 1/20/2012; 1/9/2012; 12/15/2011; 12/14/2011; 11/21/2011; 11/16/2011; 10/17/2011; 10/12/2011; 10/5/2011; 9/27/2011; 9/23/2011; 9/21/2011; 9/1/2011; 8/31/2011; 8/30/2011; 7/28/2011
Internal memoranda, telecons, etc.	NA
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg 4/20/2010
• EOP2 meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	N/A
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 8/9/2012
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 4/25/2012
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 1 PMR and 1 PMC
Clinical Information⁶	
Clinical Reviews	

⁶ Filing reviews should be filed with the discipline reviews.

<ul style="list-style-type: none"> Clinical Team Leader Review(s) <i>(indicate date for each review)</i> 	4/17/2012 Co-signed primary review
<ul style="list-style-type: none"> Clinical review(s) <i>(indicate date for each review)</i> 	Review 4/17/2012 Filing Review 9/12/2011
<ul style="list-style-type: none"> Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i> 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not <i>(indicate date of review/memo)</i> 	See 4/17/2012 Clinical Review (page 30)
<ul style="list-style-type: none"> Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i> 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i> 	<input checked="" type="checkbox"/> Not applicable
<ul style="list-style-type: none"> Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement <i>(indicate date(s) of submission(s))</i> REMS Memo(s) and letter(s) <i>(indicate date(s))</i> Risk management review(s) and recommendations (including those by OSE and CSS) <i>(indicate date of each review and indicate location/date if incorporated into another review)</i> 	NA <input type="checkbox"/> None 6/29/2012
<ul style="list-style-type: none"> OSI Clinical Inspection Review Summary(ies) <i>(include copies of OSI letters to investigators)</i> 	<input type="checkbox"/> None requested Review 3/26/2012
Clinical Microbiology <input checked="" type="checkbox"/> None	
<ul style="list-style-type: none"> Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i> 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> Clinical Microbiology Review(s) <i>(indicate date for each review)</i> 	<input checked="" type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
<ul style="list-style-type: none"> Statistical Division Director Review(s) <i>(indicate date for each review)</i> 	<input type="checkbox"/> None 4/9/2012 Co-signed primary review
<ul style="list-style-type: none"> Statistical Team Leader Review(s) <i>(indicate date for each review)</i> 	<input type="checkbox"/> None 5/2/2012
<ul style="list-style-type: none"> Statistical Review(s) <i>(indicate date for each review)</i> 	<input type="checkbox"/> None Review 4/9/2012 Filing Review 9/8/2011
Clinical Pharmacology <input type="checkbox"/> None	
<ul style="list-style-type: none"> Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i> 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i> 	<input type="checkbox"/> None 3/23/2012 Co-signed primary review
<ul style="list-style-type: none"> Clinical Pharmacology review(s) <i>(indicate date for each review)</i> 	<input type="checkbox"/> None Review 3/23/2012 Filing Review 9/16/2011
<ul style="list-style-type: none"> DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i> 	<input checked="" type="checkbox"/> None

Nonclinical		<input type="checkbox"/> None
❖ Pharmacology/Toxicology Discipline Reviews		
• ADP/T Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None
• Supervisory Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None 3/30/2012
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)		<input type="checkbox"/> None Review 4/12/2012 Filing Review 9/20/2011
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting		<input checked="" type="checkbox"/> None
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)		<input checked="" type="checkbox"/> None requested
Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None Co-signed primary review 8/6/2012, 6/15/2012; 4/13/2012;
• Product quality review(s) including ONDQA biopharmaceutics reviews (<i>indicate date for each review</i>)		<input type="checkbox"/> None Product Quality Reviews 8/6/2012; 6/15/2012; 4/13/2012 Filing Review 9/6/2011 (2) ONDQA Biopharm Review 4/11/2012 Filing Review 9/7/2011
❖ Microbiology Reviews		<input type="checkbox"/> Not needed Review 7/26/2012; 4/19/2012; 2/3/2012 Filing Review 8/31/2011
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (<i>indicate date of each review</i>) <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (<i>indicate date of each review</i>)		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (<i>indicate date of each review</i>)		<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)		See 4/12/2012 CMC Review (page 153)
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)		
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)		

❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷</i>)	Date completed: <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input type="checkbox"/> Completed <input checked="" type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Baird, Amy

From: Baird, Amy
Sent: Tuesday, July 31, 2012 10:06 AM
To: 'Tom Tarlow'
Subject: RE: Marqibo container-carton labeling

Tom,

Attached are DMEPA's and CMC's final comments on the container-carton labeling.

A. Carton Labeling

Revise the statement, (b) (4) to read, Overlabel and Infusion Bag Label. (b) (4)

B. Container Labels for Sodium Phosphate Injection, Spingomyelin-Cholesterol Liposome Injection, and Vincristine Sulfate Injection, USP

1. Revise the statement, (b) (4) to read See package insert for preparation instructions. (b) (4)
2. Switch the location of the statements, Single-Use Vial – Discard Unused Portion, and See package insert for preparation instructions.

Amy Baird

Regulatory Project Manager

Division of Hematology Products, CDER, FDA

10903 New Hampshire Ave

WO #22, Room 1223

Silver Spring, MD 20993

Telephone: 301-796-4969

Facsimile: 301-796-9845

Email: amy.baird@fda.hhs.gov

From: Tom Tarlow [mailto:TTarlow@Talontx.com]
Sent: Monday, July 16, 2012 7:09 PM
To: Baird, Amy
Subject: Marqibo container-carton labeling

Hello Amy

Final testing results of the bar code added to the Marqibo container-carton labeling were received and all passed the ANSI standard for optical scanning. Attached please find the six (6) PDF files that comprise container-carton labeling for Marqibo.

- Marqibo Carton
- VSI vial
- SCLI vial

- SPI vial
- SPI vial overlabel
- IV bag overlabel

These labels address all FDA comments from the July 10, 2012 email that contained the DMEPA and CMC final container-carton labeling comments.

I plan to inform Dr N Patel, OPDP, by separate email of Talon's plans for submission of Marqibo launch material. I will copy you.

All best

Tom

Thomas J Tarlow
Vice President
Regulatory Affairs and Quality Assurance
Talon Therapeutics, Inc (formerly Hana Biosciences)
650 228 5066 direct
650 228 5067 fax
(b) (6) cell
tom.tarlow@hanabiosciences.com

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/s/

AMY C BAIRD
07/31/2012

Baird, Amy

From: Baird, Amy
Sent: Monday, July 30, 2012 10:52 AM
To: 'Tom Tarlow'
Subject: NDA 202497 Marqibo - Updated PMR and PMCs

Tom,

We have updated PMC#3 to reflect the timeline that Talon proposed. Please review and if acceptable, follow-up with an official electronic submission to your NDA providing the commitment. Please attempt to send the submission ASAP.

PMR 1910-1

NDA	202497
Product Name:	Marqibo (vincristine sulfate liposome injection)
PMR Description:	To perform and submit the trial, presently under SPA agreement, TTX404 “A Phase 3, Multicenter, Randomized Study to Evaluate the Substitution of Marqibo (Vincristine Sulfate Liposomes Injection, VSLI) Standard Vincristine Sulfate Injection (VSI) in the Induction, Intensification, and Maintenance Phases of Combination Chemotherapy in the Treatment of Subjects > 60 Years Old with Newly Diagnosed Acute Lymphoblastic Leukemia (ALL)” to address your subpart H commitment according to the timelines below. Any amendments to the SPA trial TTX404 must all be submitted to the PMR.

PMR/PMC Schedule Milestones:	Report of 1/3 enrollment	12/2014
	Report of 2/3 enrollment	12/2015
	Report of enrollment completion	12/2016

	Study/Trial Completion			8/2017
	Final Report Submission: the final clinical study report with complete raw datasets			4/2018

PMC 1910-2

NDA	202497
Product Name:	Marqibo (vincristine sulfate liposome injection)
PMC Description:	Due to the complexity of on site preparation of the final drug product, Talon agrees to study and report at six month intervals on the experience of health care practitioners (HCPs) regarding safety or technical problems with preparation of Marqibo in practice settings.

PMR/PMC Schedule Milestones:	Preliminary protocol submission (survey and report template FDA submission)	10/2013
	Final Protocol Submission (final survey and report template FDA submission)	12/2013
	First 6 monthly report	6/2013

	Second interim report		12/2013
	Third interim report		6/2014
	Fourth interim report		12/2014
	Fifth interim report		6/2015
	Sixth interim report		12/2015
	Seventh interim report		6/2016
	Eighth interim report		12/2016
	Ninth interim report		6/2017
	Final Report		12/2017

PMC 1910-3

NDA	202497
Product Name:	Marqibo (vincristine sulfate liposome injection)
PMC Description:	Considering the relative complexity of preparation of Marqibo, Talon agrees to explore methods to simplify preparation of the final drug product, including the possibility of developing a formulation of liposomal encapsulation such that the step of heating of the drug in the pharmacy is eliminated.

PMR/PMC Schedule Milestones:	Preliminary Protocol Submission	12/2012
	Final Protocol Submission	6/2013
	Study Completion	12/2016

	Study Report Submission to FDA		6/2017
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Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
07/30/2012



NDA 202497

NDA ACKNOWLEDGMENT

Talon Therapeutics Incorporated
Attention: Thomas J. Tarlow
Vice President, Regulatory Affairs
2201 Bridgepointe Parkway, Suite 250
San Mateo, CA 94404

Dear Mr. Tarlow:

We have received your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Marqibo (Vincristine Sulfate Liposomes Injection)

Date of Application: July 12, 2011

Date of Receipt: July 12, 2011

Our Reference Number: NDA 202497

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 10, 2011, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, call Amy Baird, Regulatory Project Manager, at (301) 796-4969.

Sincerely,

{See appended electronic signature page}

Amy Baird
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

AMY C BAIRD
07/28/2011

Baird, Amy

From: Baird, Amy
Sent: Friday, July 27, 2012 10:11 AM
To: 'Tom Tarlow'
Subject: RE: NDA 202497 Marqibo - FDA PMR/PMCs

Tom,

Per the request of the FDA review team, how much (how long) stability data does Talon plan on submitting with the proposed time line?

Thanks,

Amy Baird
 Regulatory Project Manager
 Division of Hematology Products, CDER, FDA
 10903 New Hampshire Ave
 WO #22, Room 1223
 Silver Spring, MD 20993
 Telephone: 301-796-4969
 Facsimile: 301-796-9845
 Email: amy.baird@fda.hhs.gov

From: Tom Tarlow [mailto:TTarlow@Talontx.com]
Sent: Thursday, July 26, 2012 3:30 PM
To: Baird, Amy
Subject: RE: NDA 202497 Marqibo - FDA PMR/PMCs

Hello Amy

Thank you for forwarding these revised PMR/PMCs. As we discussed moments ago, there are two revisions to the schedule milestones for PMC 1910-3, "...exploration of methods to simplify preparation of the drug product..." that are concerning to Talon. The Study Completion date is shortened by one year, from 12/2016 to 12/2015 and the Study Report Submission to FDA is shortened by one year from 6/2017 to 6/2016.

These changes are perplexing to Talon. We presented the rationale for the schedule milestones for this PMC in an email on July 9 2012 (see attached) which indicated that PMR/PMCs were final. The July 9 2012 email noted that the time allotments proposed for this PMC were based upon demonstrating ICH-mandated stability data. Talon's position has not changed. We believe that real-time stability for an improved formulation is critical to assessing the feasibility of this exploration.

All best

Tom

From: Baird, Amy [mailto:Amy.Baird@fda.hhs.gov]
Sent: Thursday, July 26, 2012 11:14 AM
To: Tom Tarlow
Subject: NDA 202497 Marqibo - FDA PMR/PMCs

Tom,

As promised, below is the PMR and PMCs for NDA 202497 Marqibo. Please review and if all is acceptable, follow-up with an official submission to NDA 202497 Marqibo providing Talon's commitment.

PMR 1910-1

NDA Product Name:	202497 Marqibo (vincristine sulfate liposome injection)
	To perform and submit the trial, presently under SPA agreement, TTX404 "A Phase 3, Multicenter, Randomized Study to Evaluate

PMR Description:	the Substitution of Marqibo (Vincristine Sulfate Liposomes Injection, VSLI) for Standard Vincristine Sulfate Injection (VSI) in the Induction, Intensification, and Maintenance Phases of Combination Chemotherapy in the Treatment of Subjects > 60 Years Old with Newly Diagnosed Acute Lymphoblastic Leukemia (ALL)” to address your subpart H commitment according to the timelines below. Any amendments to the SPA trial TTX404 must also be submitted to the PMR.
------------------	--

PMR/PMC Schedule Milestones:	Report of 1/3 enrollment	12/2014
	Report of 2/3 enrollment	12/2015
	Report of enrollment completion	12/2016
Study/Trial Completion		8/2017
Final Report Submission: the final clinical study report with complete raw datasets		4/2018

PMC 1910-2

NDA Product Name:	202497 Marqibo (vincristine sulfate liposome injection)
PMR/PMC Description:	Due to the complexity of on site preparation of the final drug product, Talon agrees to study and report at six month intervals on the experience of health care practitioners (HCPs) regarding safety or technical problems with preparation of Marqibo in practice settings.

PMR/PMC Schedule Milestones:	Preliminary protocol submission (survey and report template FDA submission)	10/2012
	Final Protocol Submission (final survey and report template FDA submission)	12/2012
	First 6 monthly report	6/2013
	Second interim report	12/2013
	Third interim report	6/2014
	Fourth interim report	12/2014
	Fifth interim report	6/2015
	Sixth interim report	12/2015
	Seventh interim report	6/2016
	Eighth interim report	12/2016
	Ninth interim report	6/2017
	Final Report	12/2017

PMC 1910-3

NDA Product Name:	202497 Marqibo (vincristine sulfate liposome injection)
PMR/PMC Description:	Considering the relative complexity of preparation of Marqibo, Talon agrees to explore methods to simplify preparation of the final drug product, including the possibility of developing a formulation of liposomal encapsulation such that the step of heating of the drug in the pharmacy is eliminated.

PMR/PMC Schedule Milestones:	Preliminary Protocol Submission	12/2012
	Final Protocol Submission	6/2013
	Study Completion	12/2015
Study Report Submission to FDA		6/2016

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
07/27/2012

Baird, Amy

From: Baird, Amy
Sent: Thursday, July 26, 2012 2:14 PM
To: 'Tom Tarlow'
Subject: NDA 202497 Marqibo - FDA PMR/PMCs

Tom,

As promised, below is the PMR and PMCs for NDA 202497 Marqibo. Please review and if all is acceptable, follow-up with an official submission to NDA 202497 Marqibo providing Talon's commitment.

PMR 1910-1

NDA 202497
Product Name: Marqibo (vincristine sulfate liposome injection)

PMR Description: To perform and submit the trial, presently under SPA agreement, TTX404 "A Phase 3, Multicenter, Randomized Study to Evaluate the Substitution of Marqibo (Vincristine Sulfate Liposomes Injection, VS LI) for Standard Vincristine Sulfate Injection (VSI) in the Induction, Intensification, and Maintenance Phases of Combination Chemotherapy in the Treatment of Subjects > 60 Years Old with Newly Diagnosed Acute Lymphoblastic Leukemia (ALL)" to address your subpart H commitment according to the timelines below. Any amendments to the SPA trial TTX404 must also be submitted to the PMR.

PMR/PMC Schedule Milestones:	Report of 1/3 enrollment	<u>12/2014</u>
	Report of 2/3 enrollment	<u>12/2015</u>
	Report of enrollment completion	<u>12/2016</u>
	Study/Trial Completion	<u>8/2017</u>
	Final Report Submission: the final clinical study report with complete raw datasets	<u>4/2018</u>

PMC 1910-2

NDA 202497
Product Name: Marqibo (vincristine sulfate liposome injection)

PMC Description: Due to the complexity of on site preparation of the final drug product, Talon agrees to study and report at six month intervals on the experience of health care practitioners (HCPs) regarding safety or technical problems with preparation of Marqibo in practice settings.

PMR/PMC Schedule Milestones:	Preliminary protocol submission (survey and report template FDA submission)	<u>10/2012</u>
	Final Protocol Submission (final survey and report template FDA submission)	<u>12/2012</u>
	First 6 monthly report	<u>6/2013</u>
	Second interim report	<u>12/2013</u>
	Third interim report	<u>6/2014</u>
	Fourth interim report	<u>12/2014</u>
	Fifth interim report	<u>6/2015</u>
	Sixth interim report	<u>12/2015</u>

Seventh interim report	<u>6/2016</u>
Eighth interim report	<u>12/2016</u>
Ninth interim report	<u>6/2017</u>
Final Report	<u>12/2017</u>

PMC 1910-3

NDA 202497
Product Name: Marqibo (vincristine sulfate liposome injection)

PMC Description: Considering the relative complexity of preparation of Marqibo, Talon agrees to explore methods to simplify preparation of the final drug product, including the possibility of developing a formulation of liposomal encapsulation such that the step of heating of the drug in the pharmacy is eliminated.

PMR/PMC Schedule Milestones: Preliminary Protocol Submission 12/2012
Final Protocol Submission 6/2013
Study Completion 12/2015
Study Report Submission to FDA 6/2016

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
07/26/2012

Baird, Amy

From: Baird, Amy
Sent: Thursday, July 19, 2012 10:02 AM
To: 'Tom Tarlow'
Subject: NDA 202497 Marqibo - FDA Response re PMR for Marqibo

Importance: High

We have received and reviewed your latest submission that provides your PMR text describing the existing SPA trial, TTX404, and the modifications now proposed as part of a PMR.

Given the importance of the SPA trial, TTX404, the time remaining in the current PDUFA cycle, and our need to make any changes to an SPA protocol through a careful and deliberative internal review process, we now recommend that the PMR for the clinical trial not introduce any changes to the SPA trial in effect. The PMR for a "confirmatory" trial, as required by subpart H, will state only that the SPA trial, as agreed upon previously, is acceptable as the trial to be performed for subpart H. Amendments to the SPA trial protocol will be considered after the pending PDUFA date rather than before that date. The agency is interested in modifications to the SPA protocol but recommends that any SPA modifications be negotiated outside of the PDUFA timeclock.

The PMR now will state: You agree to perform and submit the trial, TTX404, presently under SPA agreement, as the trial to address your subpart H commitment, and according to the timeline stated below.

Any amendments to the SPA trial TTX404 protocol must also be submitted to the PMR.

Milestone	Date
Preliminary Protocol Submission (asparaginase use)	2 months following approval date – 10/2012
Final Protocol Submission	2 months following approval date – 12/2012
Report of 1/3 enrollment	28 months following approval date – 12/2014
Report of 2/3 enrollment	40 months following approval date – 12/2015
Report of enrollment completion	52 months following approval date – 12/2016
Study / Trial Completion	60 months following approval date – 8/2017
Final Report Submission: the final clinical study report with complete raw datasets	68 months following approval date – 4/2018

Please update the timeline based upon the currently proposed PMR. **Also, please send a response via email as quickly as possible. I will ask the FDA Marqibo team to review your response as quickly as possible to gain agreement. After agreement, follow-up with an official submission. The date of the submission will be referred to in the action letter.**

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
07/19/2012

Baird, Amy

From: Baird, Amy
Sent: Thursday, July 19, 2012 9:33 AM
To: 'Tom Tarlow'
Subject: NDA 202497 Marqibo - FDA Responses to 7/16/2012 Email Re Container/Carton Labeling

Tom,

The FDA team has reviewed your email dated July 16, 2012, in which Talon provided a response to the FDA comments regarding the container/carton labeling for Marqibo.

Please provide a response to these comments NLT Monday, July 23, 2012, 10:00am EST.

A. Carton Labeling

Revise the statement, (b) (4) to read, Overlabel and Infusion Bag Label.
(b) (4)

B. Container Labels for Sodium Phosphate Injection, Sphingomyelin-Cholesterol Liposome Injection, and Vincristine Sulfate Injection, USP

1. Revise the statement, (b) (4), to read See package insert for preparation instructions. (b) (4)
2. Switch the location of the statements, Single-Use Vial – Discard Unused Portion, and See package insert for preparation instructions.

Please contact me via email should you have any questions regarding these comments.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
07/19/2012

Baird, Amy

From: Baird, Amy
Sent: Thursday, June 28, 2012 11:06 AM
To: 'Tom Tarlow'
Subject: NDA 202497 Marqibo - FDA Response re Proposed PMR/PMCs

Tom,

Please refer to the NDA application for NDA 202497 Marqibo (Vincristine Sulfate Liposomes Injection) dated July 12, 2011, which provides for the proposed indication "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."

We also refer to Talon's electronic mails dated June 1 and 8, 2012, in which you provide responses to the FDA proposed PMR and PMC for Marqibo. Below is the FDA clinical team's response to your original June 1, 2012, email and some follow-up comments regarding your June 8, 2012, email.

In addition to the comments below, we are proposing an additional PMC. Please review and respond as quickly as possible with your comments.

FDA Comments regarding PMR

(b) (4)

1. The milestone times are acceptable
2. Actual dates, in the form of month and year, are necessary in the final version, predicated on an approval action
3. Based on the ODAC discussion, there may be variations among sites in use of asparaginase. Please amend the protocol to accommodate this variation. In the revised protocol, provide your plans regarding the use of asparaginase and your plans for analyzing the role of this variable on efficacy and toxicity.
4. This amended protocol must be submitted no later than 2 months after an approval date, to meet the proposed milestone time.

FDA Comments regarding PMC "Due to the complexity of on site preparation of the final drug product, you agree to study and report at six month intervals on the experience of health care practitioners (HCPs) regarding safety or technical problems with preparation of Marqibo in practice settings."

1. The milestone times are acceptable. Note that the periodic report for the interval and cumulative experience is due every 6 months for 5 years, 10 reports (unless ended sooner by FDA).
2. To allow report preparation, the first report is due to be submitted no later than 8 months following an approval date, and the final report would be due 4.5 years later.
3. The modifications to the report format and content proposed by Talon are acceptable.

Action needed: Please reply indicating your agreement with the above requirements, or advise if you have additional concerns.

FDA Additional Proposed PMC

Considering the relative complexity of preparation of Marqibo, Talon agrees to explore methods to simplify preparation of the final drug product, including the possibility of developing a formulation of liposomal encapsulation such that the step of heating of the drug in the pharmacy is eliminated.

(Note that, in this case, the term protocol refers to an action plan to achieve the goal, and study completion indicates the time when the testing of the action plan is completed.)

PMC Schedule Milestones:	Preliminary Protocol Submission	MM/YYYY
	Final Protocol Submission:	_____
	Study Completion:	_____
	Final Report Submission:	_____

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
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Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
06/28/2012

Baird, Amy

From: Baird, Amy
Sent: Tuesday, June 12, 2012 5:25 PM
To: 'Tom Tarlow'
Subject: RE: Marqibo Draft Medication Guide Revised for Readability

Tom,

Please refer to the NDA application for NDA 202497 Marqibo (Vincristine Sulfate Liposomes Injection) dated July 12, 2011, which provides for the proposed indication "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." We also refer to your e-mail dated June 7, 2012, in which you provide the revised "Medication Guide".

The FDA review team has completed a review of your proposed document and have the following comments:

1. The document should be titled: "Patient Information" and not [REDACTED] (b) (4) ". All the patient information documents are under review, and a revised format may be identified. However, until such time, the Marqibo patient advice form is most appropriately titled "Patient Information".
2. All of the information [REDACTED] (b) (4) regarding peripheral neuropathy, is to be placed [REDACTED] (b) (4) at the beginning of the section "What are the possible side effects of Marqibo?"

The following points also remain to be resolved:

- choose 1 term, either doctor or healthcare provider and use it consistently throughout the document. In several places we note that you use "doctor, nurse, or health care provider." In general, since patients may see an NP or PA and not always a doctor, we recommend using "healthcare provider"; however, you may use "doctor."
- avoid using "and/or," "his/her," etc. as these may be difficult for patients to understand.
- Use patient-friendly language. For example, instead of the word "potential" use "possible."
- In the section "What are the possible side effects of Marqibo?" serious side effects should be listed first, followed by the common side effects. The list of serious side effects should start with the most serious, and include all of the side effects that are listed in the Warnings and Precautions (section 5) of the drug label.
- The list of common side effects should be based on the common side effects listed in highlights and in PI section 6.1 (usually in the table) and should not be a laundry list based on body systems.

Please submit a revised document based upon our comments as soon as possible.

Regards,

Amy Baird

Regulatory Project Manager

Division of Hematology Products, CDER, FDA

10903 New Hampshire Ave

WO #22, Room 1223

Silver Spring, MD 20993

Telephone: 301-796-4969

Facsimile: 301-796-9845

Email: amy.baird@fda.hhs.gov

From: Tom Tarlow [mailto:TTarlow@Talontx.com]

Sent: Thursday, June 07, 2012 1:10 PM

To: Baird, Amy

Subject: Marqibo Draft Medication Guide Revised for Readability

Hello Amy

You provided a request for increased readability for the draft Marqibo Medication Guide on Apr 5, 2012 (see attached). We located and contracted with a provider of these services and have received a revised draft Marqibo Medication Guide. The improvement in readability is approximately one grade level (The new scores are a 9th grade level (9.1 vs. 10.2 before) and reading ease score of 49.7 (vs. 42.7)). In order to increase readability further, more substantial revisions to the risk and safety language would have to be made to shorten and simplify the Guide. Can you present this revised Word 2003 track changes version to your team to find out whether they favor further revisions or whether the current version has value?

Thanks

Tom

Thomas J Tarlow

Vice President

Regulatory Affairs and Quality Assurance

Talon Therapeutics, Inc (formerly Hana Biosciences)

650 228 5066 direct

650 228 5067 fax

(b) (6) cell

tom.tarlow@hanabiosciences.com

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/s/

AMY C BAIRD
06/12/2012

Baird, Amy

From: Baird, Amy
Sent: Friday, June 08, 2012 11:02 AM
To: 'Tom Tarlow'
Subject: NDA 202497 Marqibo - PMC Regarding Safety

Tom,

Please refer to the NDA application for NDA 202497 Marqibo (Vincristine Sulfate Liposomes Injection) dated July 12, 2011, which provides for the proposed indication "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."

We also refer to Talon's electronic mail dated June 1, 2012, in which you provide responses to the FDA proposed PMR and PMC for Marqibo. Below is the FDA Office of Surveillance and Epidemiology's response to your June 1, 2012, electronic email. Please note that the text below is regarding the safety PMC, not the clinical PMR.

Survey of post-marketing experience of Marqibo preparation in practice settings:

Due to the complexity of on site preparation of the final drug product, you agree to study and report at six month intervals on the experience of health care practitioners (HCPs) regarding safety or technical problems with preparation of Marqibo in practice settings.

(b) (4)

Sponsor Comment (general): Talon agrees to provide summary reports of regarding Marqibo pharmacy constitution experience as requested.

(b) (4)

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Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
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Telephone: 301-796-4969
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/s/

AMY C BAIRD
06/08/2012

Baird, Amy

From: Baird, Amy
Sent: Wednesday, May 23, 2012 12:35 PM
To: 'Tom Tarlow'
Subject: NDA 202497 Marqibo - PMC Request

Tom,

Please refer to the NDA application for NDA 202497 Marqibo (Vincristine Sulfate Liposomes Injection) dated July 12, 2011, which provides for the proposed indication "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."

The Division of Hematology Products has determined that additional postmarketing information is required, should a favorable action occur. Below is a PMC for safety. We require Talon's written agreement to commit to fulfill this request as part of the FDA's review of your application. We encourage you to enhance the description further to improve the final product's data and evidence to be obtained. Upon mutual agreement of the wording in the PMC below, we will ask you to submit an official correspondence to the NDA with a statement that you agree to perform the PMC as described and within the timelines that you specify. For initial planning purposes, you may propose tentative milestone times based on a time interval that would be feasible following an approval action date. Final PMR designation numbers will be assigned later.

There may be additional PMRs or PMCs as we continue our review.

Survey of post-marketing experience of Marqibo preparation in practice settings:

Due to the complexity of on site preparation of the final drug product, you agree to study and report at six month intervals on the experience of health care practitioners (HCPs) regarding safety or technical problems with preparation of Marqibo in practice settings. (b) (4)

(b) (4)

The study will continue for 5 years unless terminated sooner by FDA.

PMC Schedule Milestones:	Preliminary study Protocol Submission	<u>By 2 months post approval</u>
	Final Protocol Submission:	<u>By 4 months post approval</u>
	Interim study reports	<u>Every 6 months</u>
	Study Completion:	<u>08/201?</u>
	Final Report Submission:	<u>MM/YYYY</u>

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
 Regulatory Project Manager
 Division of Hematology Products, CDER, FDA
 10903 New Hampshire Ave
 WO #22, Room 1223
 Silver Spring, MD 20993
 Telephone: 301-796-4969
 Facsimile: 301-796-9845
 Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
05/23/2012

Baird, Amy

From: Baird, Amy
Sent: Friday, May 18, 2012 2:19 PM
To: 'Tom Tarlow'
Subject: NDA 202497 Marqibo - PMR Request

Tom,

Please refer to the NDA application for NDA 202497 Marqibo (Vincristine Sulfate Liposomes Injection) dated July 12, 2011, which provides for the proposed indication "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."

As we continue our review of your NDA, our policy is to manage necessary post-marketing studies and labeling so that these issues can be completed in advance of any action date. Based on the data available to date, we have determined that the following clinical trial is necessary as a post-marketing requirement (PMR), should a favorable action occur. This brief summary is intended to describe the main trial characteristics of interest. Please provide edits and comments to clarify mutually acceptable descriptions of the key trial elements. We are available to discuss by t-con if needed.

Upon mutual agreement of a draft synopsis, we will ask you to submit an official copy of the PMR trial to the NDA with a statement that you agree to perform the trial as described and within the timelines that you specify for the trial. For initial planning purposes, you may propose tentative milestone times based on a time interval that would be feasible following an approval action date. Final PMR designation numbers will be assigned later.

There may be additional PMRs or PMCs as we continue our review.



(b) (4)

PMR	Preliminary protocol submission	2 months following date of approval
Schedule Milestones:		
	Final Protocol Submission: depends on approval time	2 months later
	Report of 1/3 enrollments	16 months later
	Report of 2/3 enrollments	28 months later
	Report of enrollment completion	40 months later
	Study / Trial Completion:	48 months later
	Final Report Submission: the final clinical study report and with complete raw datasets	56 months later

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
05/18/2012



NDA 202497

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Talon Therapeutics Incorporated
Attention: Thomas J. Tarlow
Vice President Regulatory Affairs
2201 Bridgepointe Parkway
Suite 250
San Mateo, CA 94404

Dear Mr. Tarlow:

Please refer to your July 21, 2011, New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Marqibo (Vincristine Sulfate Liposomes Injection).

On April 19, 2012, we received your April 19, 2012, solicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is August 12, 2012.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by June 12, 2012.

If you have any questions, call Amy Baird, Regulatory Project Manager, at (301) 796-4969.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, M.D.
Acting Division Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ROBERT C KANE
05/03/2012

Baird, Amy

From: Baird, Amy
Sent: Wednesday, April 25, 2012 3:30 PM
To: 'Tom Tarlow'
Subject: NDA 202497 Marqibo - FDA Requests for Information

Tom,

Please refer to the NDA application for NDA 202497 Marqibo (Vincristine Sulfate Liposomes Injection) dated July 12, 2011, which provides for the proposed indication "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."

Please provide response to the following DMEPA, Microbiology and CMC requests for information.

DMEPA

Subsequent to the April 24, 2012 meeting, we request the following information regarding the clinical sites that prepared Marqibo in your clinical trials.

1. Describe the clinical sites with regard to type of facility (for example, teaching hospital, community hospital, outpatient oncology clinic).
2. How did you determine if a facility was USP 797 compliant for Pharmaceutical Compounding – Sterile Preparations?
3. Where was the water bath placed to comply with USP 797 and ensure sterility was maintained?
4. How did you determine if a site and personnel were qualified to prepare this drug?
5. Describe who prepared Marqibo with regard to their professional title (for example pharmacists, investigational pharmacists, oncology pharmacists, pharmacy technicians, or oncology nurses). Did test sites have a designated investigational pharmacist to prepare Marqibo? If yes, was Marqibo prepared in the investigational pharmacy or in the same area as all sterile intravenous products?
6. NIOSH recommends preparation of hazardous drugs in a controlled and contained environment where air pressure is negative to the surrounding areas or that is protected by an airlock or anteroom is preferred. Positive-pressure environments for hazardous drug compounding should be avoided or the work area should be augmented with an appropriately designed antechamber because of the potential spread of airborne contamination from contaminated packaging, poor handling technique, and spills in a biohazard hood. Describe the preparation process that occurred at the test sites vis-à-vis use of negative and positive-pressure environments and cabinets. What cabinets were used by the test sites to prepare Marqibo? Did the test sites use a Class I BSC, Class II or III BSC or an isolator to prepare Marqibo? Describe the movement of the product in and out of these cabinets/environments during the preparation process.
7. How did the time required to prepare Marqibo (approximately 60 to 90 minutes) impact workflow? What issues did facilities face by incorporating the preparation of Marqibo into their daily workflow?
8. Did the person preparing Marqibo perform any other functions or tasks during preparation of the Marqibo? If so, describe the other tasks performed while Marqibo was being prepared.
9. Which steps of the Marqibo preparation process do you think are most vulnerable to medication errors?
10. What processes or policies would a facility need to implement to assure Marqibo is prepared correctly?

Microbiology

SCLI Injection, manufacturer: Cangene

(b) (4)

SPI Injection, manufacturer: Jubilant HolisterStier

Chemistry, Manufacturing, and Controls (CMC)

Include the proposed acceptance limit for individual unspecified degradation products of no more than [redacted] in the specification table for SCL. (b) (4)

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
04/25/2012

Baird, Amy

From: Baird, Amy
Sent: Wednesday, April 18, 2012 10:13 AM
To: 'Tom Tarlow'
Subject: NDA 202497 Marqibo - FDA IR Letter dated 3/28/2012

Please refer to the NDA application for NDA 202497 Marqibo (Vincristine Sulfate Liposomes Injection) dated July 12, 2011, which provides for the proposed indication "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."

Also, we refer to the FDA Information Request letter dated March 28, 2012. Below are some of the deficiencies which are still pending. Please provide a submission which addresses these deficiencies no later than 12:00pm EST, April 20, 2012.

CMC

1. 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.

2. Include the proposed acceptance limit for unspecified degradation products of no more than [REDACTED] (b) (4) [REDACTED] in the table for SCLI specification.

3. 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.

Micobiology

1. For the constitution of the Marqibo kit, the contents of three separate sterile vials will be combined in the VSLI vial, heated at $65 \pm 2^\circ\text{C}$ in a water bath for the eventual administration of the admixture with 5% Dextrose Injection or 0.9% Sodium Chloride Injection. Explain what precautions will be taken to ensure that aseptic conditions will be maintained throughout the constitution process, in a pharmacy setting. An established procedure should be in place to assure that the water bath, the sterile product vials, sterile syringes and venting filters remain free of microbial contamination.

As the FDA review of NDA 202497 Marqibo is still pending, additional requests for information or deficiencies may be communicated.

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird

Regulatory Project Manager

Division of Hematology Products, CDER, FDA

10903 New Hampshire Ave

WO #22, Room 1223

Silver Spring, MD 20993

Telephone: 301-796-4969

Facsimile: 301-796-9845

Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
04/19/2012

Baird, Amy

From: Baird, Amy
Sent: Tuesday, April 17, 2012 4:14 PM
To: 'Tom Tarlow'
Subject: NDA 202497 Marqibo - FDA Comments re Human Factors Study
Attachments: image001.png

Tom,

Please refer to the NDA application for NDA 202497 Marqibo (Vincristine Sulfate Liposomes Injection) dated July 12, 2011, which provides for the proposed indication "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."

Please see DMEPA comments below regarding the Human Factors Study. These comments will be used as the basis for discussion at the April 24, 2012, meeting.

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird

[DMEPA Comments:](#)

(b) (4)





(b) (4)

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/s/

AMY C BAIRD
04/19/2012

Ferrara, Theresa

From: Ferrara, Theresa
Sent: Wednesday, April 11, 2012 4:53 PM
To: 'Tom Tarlow'
Cc: Baird, Amy
Subject: NDA 202497 Marqibo carton & container deficiencies
Importance: High

Dear Tom,

Please refer to NDA 202497 Marqibo (Vincristine Sulfate Liposomes Injection) submitted July 12, 2011. Listed below are labeling deficiencies identified by reviewers in DMEPA and ONDQA for the carton and container labels. Please review the deficiencies and submit an amendment to your application that contains revised carton and container labels. Thank you.

[Sodium Phosphate Injection Container Label](#)

1. Change the name from Sodium Phosphate Injection to Sodium Phosphate Injection, USP
2. Include the name of the manufacturer.

[Sphingomyelin-Cholesterol Liposome Injection Container Label](#)

3. Change the name from Sphingomyelin-Cholesterol Liposomes Injection to Sphingomyelin-Cholesterol Liposome Injection. Note the deletion of the letter 's' from the word *Liposomes* to read as *Liposome*.
4. Include the name of the manufacturer.

[Vincristine Sulfate Injection Container Label](#)

5. Change the name from Vincristine Sulfate Injection to VinCRISTine Sulfate Injection, USP
6. Include the name of the manufacturer.

[Marqibo Carton Label](#)

7. On the front and side panels, change the proprietary and established names from
Marqibo
Vincristine Sulfate Liposomes Injection

to read as follows:

Marqibo
(vinCRISTine sulfate LIPOSOME injection)

8. Delete the statement [REDACTED] (b) (4) from the front and side panels.
9. Front panel change the Kit Contents to (changes are underlined):
Marqibo Kit Contents
Sodium Phosphate Injection, USP vial 355 mg/25 mL (14.2 mg/mL)
Sphingomyelin-Cholesterol Liposome Injection vial 103 mg/mL
VinCRISTine Sulfate Injection, USP vial 5 mg/5 mL (1 mg/mL)
10. Include the quantitative ingredient information
11. Include the name of the manufacturer.
12. Include the lot # and expiration date.
13. Change the statement, [REDACTED] (b) (4) to read as follows:

Single Use Vial – Discard Unused Portion

14. Left panel, change that statement, [REDACTED] (b) (4)

to read as follows:

Marqibo is prepared from the components in the Marqibo kit according to the instruction in the package insert. Following preparation Marqibo must be diluted before use.

Vincristine Sulfate Liposome Injection Overlabel

15. Change the proprietary and established names from
Marqibo
Vincristine Sulfate Liposomes Injection
to read as follows:
Marqibo
(vinCRISTine sulfate LIPOSOME injection)
16. Change the strength from 0.16 mg/mL to read as follows:
5 mg/31 mL (0.16 mg/mL).
17. Remove the highlight the following statement; "Heat at 63° C to 67° C."
18. Include the name of the manufacturer.
19. Add the statement, Single Use Only – Discard Unused Portion

Marqibo IV Bag Label

20. Change the name from
Marqibo
Vincristine Sulfate Liposomes Injection
to read as follows:
Marqibo
(vinCRISTine sulfate LIPOSOME injection)

Please contact myself or Amy should you have any questions.

Kind regards,
Theresa

Theresa Ferrara, MPH
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
email: Theresa.Ferrara@fda.hhs.gov
phone: 301-796-2848

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/s/

THERESA A FERRARA
04/11/2012

Baird, Amy

From: Baird, Amy
Sent: Thursday, April 05, 2012 9:48 AM
To: 'Tom Tarlow'
Subject: NDA 202497 Marqibo - Clarification Re FDA Email dated 3/30/2012

Tom,

Please refer to the NDA application for NDA 202497 Marqibo (Vincristine Sulfate Liposomes Injection) dated July 12, 2011, which provides for the proposed indication "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."

Also, refer to the FDA email dated March 30, 2012, 2:00pm, which contained requests for labeling revisions. Below are comments that are meant to clarify our labeling request regarding Section 17 of the package insert.

The Medication Guide should be revised as follows:

1. Replace the Medication Guide with a Patient Package Insert (PPI), because a MG is not necessary for this product.
2. The Medication Guide submitted has a Flesch Reading Grade Level: 10.1 and Reading Ease Score: 45.2%. To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. Please simplify the language so that the readability scores are within this range.
3. The PPI Insert does not need the section "What is the most important information I should know about Marqibo?" The information about neuropathy can go at the beginning of the PPI section "What are the possible side effects of Marqibo?" In that section, serious side effects should be listed first based on PI section 5 (Warnings and Precautions), followed by a list of common side effects.

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
04/05/2012

Baird, Amy

From: Baird, Amy
Sent: Thursday, April 05, 2012 9:36 AM
To: 'Tom Tarlow'
Subject: NDA 202497 Marqibo - DMEPA Comments

Tom,

Please refer to the NDA application for NDA 202497 Marqibo (Vincristine Sulfate Liposomes Injection) dated July 12, 2011, which provides for the proposed indication "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."

We also refer to your submission dated January 25, 2012, containing the Human Factors (HF) Study. Please see below for comments from DMEPA.

(b) (4)



In a March 28, 2012 correspondence, we requested additional HF studies. We did not have sufficient time to discuss the expectations of this study at the April 2, 2011 meeting. Therefore we provide the following comments concerning the HF study. The HF study should include the following:

(b) (4)

Furthermore, we request you prepare the following upon approval of your product:

1. Notify healthcare professionals by way of a letter of the differences of your product compared to non-liposomal vincristine sulfate.
2. Notify major drug reference publishers, such as Thomson Reuters, Wolters Kluwer, and Lexi-Comp, of the introduction of Marqibo and request they differentiate Marqibo from non-liposomal vincristine sulfate.

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
04/05/2012



NDA 202497

INFORMATION REQUEST

Talon Therapeutics Incorporated
Attention: Thomas J. Tarlow
Vice President Regulatory Affairs
2201 Bridgepointe Parkway
Suite 250
San Mateo, CA 94404

Dear Mr. Tarlow:

Please refer to your New Drug Application (NDA) dated July 12, 2011, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Marqibo (Vincristine Sulfate Liposomes Injection). We also refer to your submissions dated January 25, February 13 and 28, and March 14, 2012.

As part of our ongoing review of your application, we have identified deficiencies that preclude discussion of labeling and postmarketing requirements/commitments at this time.

This notification does not reflect a final decision on the information under review.

Please review the following comments and information requests. We request a written response by close of business April 5, 2012, in order to continue our evaluation of your NDA.

Chemistry, Manufacturing, and Control (CMC)

1. The requested VSI impurity profile comparison between your VSI lots and RLD was not provided in the amendment. 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 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. We recommend the following acceptance criteria for the *in vitro* release testing (with the differences from the proposed highlighted).

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

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 FDA Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications (7/1998) available at <http://www.fda.gov/cder/guidance/index.htm#chemistry>.

5. Submit the updated drug product specification tables for SCLI and VSLI that reflect all changes.

Microbiology

Please refer to our electronic communication dated February 9, 2012, requesting information pertaining to two Microbiology questions. Your response to question 1 is incomplete and our communication is being re-sent for your response.

1. For the constitution of the Marqibo kit, the contents of three separate sterile vials will be combined in the VSLI vial, heated at $65 \pm 2^{\circ}\text{C}$ in a water bath for the eventual administration of the admixture with 5% Dextrose Injection or 0.9% Sodium Chloride Injection. Explain what precautions will be taken to ensure that aseptic conditions will be maintained throughout the constitution process, in a pharmacy setting. An established procedure should be in place to assure that the water bath, the sterile product vials, sterile syringes and venting filters remain free of microbial contamination.

Division of Medication Error Prevention and Analysis (DMEPA)

The safety of your proposed product is critically dependent upon the accurate compounding of the liposomal formulation. Specifically, deviating from the specified procedures regarding the time and temperature ranges would result in decreased encapsulation of vincristine and therefore considerably more free vincristine in solution. This represents a critical safety concern as the dosing and administration for the liposomal formulation is dependent upon the near complete encapsulation of vincristine. The greater amount of free vincristine would cause a serious risk to patients since the liposomal formulation is dosed considerably higher than the non-liposomal formulation of vincristine. We are concerned that your preparation procedures are prone to deviations and errors because they are exceedingly complex and will require a change in current pharmacy practice. In addition to these concerns regarding the compounding of your product, we have other medication error concerns with potential confusion between your vincristine

sulfate liposome injection and the currently marketed non-liposome vincristine sulfate injection. Our concerns are further described below along with steps you should take to improve the safe use of this product.

1. Concerns with Equipment

a. Availability of Equipment

We are not aware of any other marketed drug product that requires heating in a water bath in the US marketplace. We are also unaware of any product that has specified duration of time and temperature exposures during routine compounding. Therefore, we have concerns that the equipment including hot water bath, calibrated thermometer, and timer necessary for preparation are not typically available in inpatient pharmacies, outpatient chemotherapy centers or general oncology practices.

b. Use of Equipment

Because the equipment used to compound this drug is not typically used by pharmacy staff or other healthcare providers, the staff may lack the ability or technical expertise to use this equipment as described. Additionally, environmental influences may further interfere with the correct use of the equipment, including work place interruptions and inadequate staffing as well as sterility recommendations required by USP 797 and the Joint Commission for intravenous product preparation.

c. Maintenance of Equipment

Because this equipment is not readily available, there will be no prior knowledge of how often the equipment requires maintenance, calibration or replacement. Additionally there are no instructions in the event the equipment malfunctions during product preparation.

Your current submission does not adequately address the aforementioned concerns. Therefore, we request the following:

- a. Describe how you plan to mitigate the aforementioned concerns.
- b. As part of your plan, we ask that you provide data to support that the product can be prepared safely in the event the equipment fails or the preparation time or temperature exceeds the recommendations provided in the labeling.

c.  (b) (4)

(b) (4)

- d. Instructions for the water bath are complicated with regard to preventing the water from going below 3.2 inches, getting too hot, and rising rapidly beyond the set-point. Please clarify how any variance to these parameters affect encapsulation of vincristine. Also clarify how preparers should adjust the temperature so that the water does not get too hot or rise rapidly beyond the set-point.

2. Procedure for Preparing Liposomal Formulation

Your constitution procedures are very complex and appear to require a substantial amount of pharmacy/healthcare personnel time and attention to ensure accurate encapsulation. Additionally, this product requires preparation by combining the contents of 3 vials and heating to a specific range of temperature and amount of time, which is not a part of current pharmacy practice. Furthermore, for patients with a body surface area greater than 2.2 m^2 , doses greater than 5 mg may be required. In these cases two Marqibo Kits will be required for reconstitution.

We doubt the capability of general oncology practices and general hospital pharmacies to acquire and possess the skills and conditions for routinely and safely preparing of the drug. While some pharmacy survey information is available, we are not assured that the pharmacies studied can be considered to represent and confirm that the general preparation of Marqibo can routinely be performed with sterility and safety in diverse settings.

To ensure the aforementioned concerns are addressed we request the following:

- a. Please provide further evidence and justification that facilities other than specialized pharmacy facilities can routinely and consistently accomplish the steps necessary to deliver a safe drug product to the patient's bedside. Consult with stakeholder groups as part of your human factors assessment (e.g., The American Society of Health-System Pharmacists, International Society of Oncology Pharmacy Practitioners, The Oncology Nursing Society, Institute of Safe Medication Practices, Joint Commission, and American Society of Clinical Oncology) to determine whether these groups consider the preparation required to be within the scope of practice for healthcare providers or their members, and to seek input regarding any concerns the organizations might have regarding the introduction of a product requiring such an intensive preparation procedure.

Additionally, to support that providers can prepare this product safely, you should conduct further human factors studies that demonstrate preparers can accomplish the steps necessary to encapsulate vincristine.

- b. Clarify whether the hot water bath is to be placed in the sterile product hood or on a counter. If it's to be placed in a sterile product hood, how will the bath be used in a barrier isolator or glove box?
- c. State how the preparer removes the vial from the hot water bath. Are tongs required to prevent burning from hot water bath?
- d. State how many minutes the preparer must allow the vial to cool to room temperature prior to further reconstitution in the intravenous bag.
- e. Currently, the insert labeling recommends the preparer invert the vial 5 times during preparation. (b) (4)

3. Confusion between Liposomal and Non-liposomal Formulations

We have reviewed post-marketing medication error reports involving confusion between the non-liposomal and liposomal formulations of amphotericin, doxorubicin, and daunorubicin that have resulted in patient harmful and fatalities. Specifically, overdoses resulted from confusion between the different formulations and dosing, nomenclature and packaging, as well as similar storage. We anticipate similar errors with the introduction of this liposomal product. We also anticipate errors in the pediatric population if this liposomal product is used off label because the doses for the non-liposomal product overlap with the liposomal product of vincristine sulfate.

Your current submission does not adequately address these aforementioned errors. Describe how you plan to mitigate these risks.

4. Labels and Labeling Recommendations

We provide the following recommendations for the currently proposed labeling. Additional recommendations may follow once we have evaluated the human factors assessment and proposed revisions based on the aforementioned safety concerns.

- a. General Comments for all Container Labels and Carton Labeling
 - i. In addition to the utilization of Tallman Lettering the established name (i.e., VinCRISTine Sulfate LIPOSOMES Injection), further features should be utilized to improve differentiation of this product from conventional Vincristine Sulfate. These features should be evaluated as part of the human factors assessment.
 - ii. Revise the warning statement concerning the route of administration to read as follows:

For Intravenous Use Only
Fatal If Given by Other Routes

b. Comments for Container Label

i. General comments for all three vial labels

A. The vial labels provided in the sample kit differ from the labels provided in the application. [REDACTED] (b) (4)

[REDACTED]. Please clarify this discrepancy.

B. Revise the statement [REDACTED] (b) (4) to read as follows:

Single Use Vial- Discard Unused Portion

ii. Container Label for Vincristine Sulfate

Revise the statement of strength to display the total drug content per total volume followed by the concentration per mL. For example:

5 mg/5 mL
(1 mg/mL)

iii. Container Label for Sodium Phosphate vial

Revise the statement of strength to display the total drug content per total volume followed by the concentration per mL. For example:

355 mg/25 mL
(14.2 mg/mL)

c. Carton Labeling

i. Revise the presentation of the proprietary and established names to read as follows:

[REDACTED] (b) (4)

ii. Place the storage instructions [2° C to 8° C (36° F to 46° F)] on the principal display panel.

- iii. Revise the statement of strength for each component of the Kit to reflect the total drug content per total volume followed by the concentration per mL as described above.

- d. Over Labeling

Revise the listing of temperature and time to read:
Temp In:
Time In:
Temp Out:
Time Out:

- e. Intravenous Bag Label

Revise the statement (b) (4) to read “Expiration date and time”.

- f. Insert Labeling
 - i. Dosage and Administration, Dose Delays, Dose Modifications, and Radiation Therapy, Section 2.4 - Improve the presentation of dose modifications. Currently the non-hematologic toxicity dose modifications are difficult to locate in the Dose Reductions Schematic in Figure 1. The dose modifications should be placed in sentence format following the section header so that healthcare practitioners can easily locate this information.
 - ii. Constitution Instructions for Marqibo, Section 2.7 - The preparation instructions are difficult to follow because the text is crowded and appears in one long paragraph. To improve readability and comprehension of these instructions number each step (e.g., Step 1, Step 2).
 - iii. The insert abbreviates the drug names for the components of this product. We request you remove the abbreviations (VSI, SCLI, and SPI) and spell out each name in its entirety (Vincristine Sulfate Injection, Sphingomyelin/Cholesterol Liposomes Injection, and Sodium Phosphate Injection.)
 - iv. The insert contains trailing zeros to denote volume measurements (1.0 mL, 3.0 mL, and 5.0 mL). Trailing zeros are considered dangerous abbreviations that have lead to ten fold dosing errors. Remove all trailing zeros.

Clinical

During the recent ODAC meeting on March 21, 2012, concerns were raised regarding the feasibility of your proposed trial to demonstrate clinical benefit. Your randomized controlled trial comparing Marqibo with vincristine designed to demonstrate an improvement in overall survival in patients aged 60 or older incorporates L-asparaginase into the first three cycles. In

particular, your consultant, Dr. Susan O'Brien, at the ODAC meeting stated that older patients do not typically receive asparaginase products due to asparaginase's well-known toxicities. This statement suggests that the study as designed may not accrue sufficiently and demonstrate Marqibo's clinical benefit. Therefore, submit a new randomized controlled trial proposal to demonstrate clinical benefit.

If you have any questions, call Amy Baird, Regulatory Project Manager, at (301) 796-4969.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, M.D.
Acting Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

AMY C BAIRD
03/28/2012
Signing For Ann Farrell

Baird, Amy

From: Baird, Amy
Sent: Friday, March 30, 2012 1:36 PM
To: 'Tom Tarlow'
Subject: NDA 202497 Marqibo - Information Request re Labeling

Tom,

Please refer to the NDA application for NDA 202497 Marqibo (Vincristine Sulfate Liposomes Injection) dated July 12, 2011, which provides for the proposed indication "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."

Please provide a response to the following requests NLT Tuesday, April 3, 2012.

1. Refer to section 7.2 of the proposed labeling which reads as follows:

7.2 P-glycoprotein Interactions

Vincristine is also a substrate for P-glycoprotein (P-gp). The effect of concomitant use of potent P-gp inhibitors or inducers has not been investigated; it is likely that these agents will alter the pharmacokinetics or pharmacodynamics of Marqibo®. Therefore the concomitant use of potent P gp inhibitors or inducers should be avoided.

Please provide a reference in support of this statement.

2. Figure 1 under Section 2-Dosage and Administration, is confusing. Please refer to the package insert for Velcade and revise this section accordingly. When responding to this request, only provide this particular section of the labeling, not the entire label.

3. In the cover letter to your NDA application you reference the non-approved NDA 021600. Can you please provide a list of information that you are cross referencing in this application?

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
03/30/2012

Baird, Amy

From: Baird, Amy
Sent: Friday, March 30, 2012 4:44 PM
To: 'Tom Tarlow'
Subject: NDA 202497 Marqibo - Clinical Information Request

Tom,

Please refer to the NDA application for NDA 202497 Marqibo (Vincristine Sulfate Liposomes Injection) dated July 12, 2011, which provides for the proposed indication "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."

Per the request of the FDA clinical review team, please provide a response to the following.

HBS407 study report stated that the AEs were assessed by NCI CTCAE v3 and were coded using MedDRA 12.1 according to the statistical analysis plan. Please provide details on how your data were collected and coded for safety analyses. Please also provide raw datasets.

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
03/30/2012

Baird, Amy

From: Baird, Amy
Sent: Friday, March 30, 2012 2:00 PM
To: 'Tom Tarlow'
Subject: NDA 202497 Marqibo - Additional Labeling Requests

Please refer to the NDA application for NDA 202497 Marqibo (Vincristine Sulfate Liposomes Injection) dated July 12, 2011, which provides for the proposed indication "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."

Please refer to the proposed labeling submitted with your application. Specifically, refer to Section 17 - Medication Guide. Section 17 requires several revisions, please refer to the labeling guidance. Section 17 is text for physicians to advise patients. In addition to the Medication Guide, we ask that you also create a Patient Package Insert. Please provide the Patient Package Insert and revisions to Section 17 as soon as possible.

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
03/30/2012



NDA 202497

INFORMATION REQUEST

Talon Therapeutics, Inc.
Attention: Thomas J. Tarlow
Vice President of Regulatory Affairs
2207 Bridgepointe Pky. Suite 250
San Mateo, CA 94404

Dear Mr. Tarlow:

Please refer to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Marqibo[®] (Vincristine Liposomal Injection) 0.16 mg/mL.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. After reviewing your amendment (No. 12) dated Mar 14, 2012 that contains responses to FDA's IR letter dated January 9, 2012, we have identified the following outstanding deficiencies:

1. The requested VSI impurity profile comparison between your VSI lots and RLD was not provided in the amendment. 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. We recommend the following acceptance criteria for the in vitro release testing (with the differences from the proposed highlighted).

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

4. Submit the updated drug product specification tables for SCLI and VSLI that reflect any changes made.

If you have questions, call Jewell Martin, Regulatory Project Manager, at (301) 301-2072.

Sincerely,

{See appended electronic signature page}

Sarah C. Pope Miksinski, Ph.D.
Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

HARIPADA SARKER

03/26/2012

Acting for Sarah Pope Miksinski

Baird, Amy

From: Baird, Amy
Sent: Thursday, March 22, 2012 11:47 AM
To: 'Tom Tarlow'
Subject: NDA 202497 Marqibo - Pharmacist Instructional Video

Tom,

Please refer to the NDA application for NDA 202497 Marqibo (Vincristine Sulfate Liposomes Injection) dated July 12, 2011, which provides for the proposed indication "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."

Per the request of the FDA review team, please provide the information that will be provided to pharmacists regarding the preparation of Marqibo. Will an instructional video be available online for pharmacists?

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
03/22/2012

Baird, Amy

From: Baird, Amy
Sent: Thursday, March 15, 2012 12:01 PM
To: 'Tom Tarlow'
Subject: NDA 202497 Marqibo - FDA Request

Tom,

Please refer to the NDA application for NDA 202497 Marqibo (Vincristine Sulfate Liposomes Injection) dated July 12, 2011, which provides for the proposed indication "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."

Per the request of the FDA review team, provide the following by COB Monday, March 19, 2012.

A sample package of Marqibo Kit as Talon intends to package the product. Additionally, the vials must not contain any drug.

Please provide the sample package via courier directly to myself at the address below.

Amy Baird
Food and Drug Administration
10903 New Hampshire Ave
WO#22, Room 1223
Silver Spring, MD 20993

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
03/15/2012

Baird, Amy

From: Baird, Amy
Sent: Thursday, March 15, 2012 10:01 AM
To: 'Tom Tarlow'
Subject: NDA 202497 Marqibo - Phase 3 Confirmatory Study

Tom,

Please refer to the NDA application for NDA 202497 Marqibo (Vincristine Sulfate Liposomes Injection) dated July 12, 2011, which provides for the proposed indication "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."

Per the request of the FDA clinical review team, provide a response to the following request by COB today, March 15, 2012.

Please update the status of your confirmatory Study TTX404. Please provide the following information: How many patients to date have been enrolled in the Study TTX404 and to which sites? How many active sites are open to date for enrollment into Study TTX404? What is the estimated time of completion for Study TTX404?

Or is the current status the same as Talon reported on February 22, 2012?

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
03/15/2012

From: [Martin, Jewell](#)
To: ["Tom Tarlow";](#)
cc: [Baird, Amy;](#)
Subject: Marqibo NDA 202497 CMC Information Request
Date: Tuesday, March 13, 2012 11:34:00 AM
Attachments: [EA Review Requirements for Drugs Derived from Plant Sources.pdf](#)

Hello Mr.. Tarlow,

Please refer to NDA 202497, we have the following request for information. Submit your response to your NDA no later than March 19, 2012.

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.

Please send a courtesy copy of your response to jewell.martin@fda.hhs.gov.

Best,

Jewell

Jewell D. Martin, MA, MBA, PMP

Product Quality Regulatory Project Manager
Office of New Drug Quality Assessment (ONDQA)
Division of New Drug Quality Assessment (DNDQA1)
Food and Drug Administration
White Oak Building 21, Rm 2625
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

(301) 796-2072
jewell.martin@fda.hhs.gov

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FDA/CENTER FOR DRUG EVALUATION AND RESEARCH

ENVIRONMENTAL ASSESSMENTS / USE OF FLORA

Source: Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications (7/1998) <http://www.fda.gov/cder/guidance/index.htm#chemistry>

I. NDA and ANDA APPLICATIONS

a. Cultivated Plants

Actions involving drug or biologic products derived from cultivated plants (e.g., grown in plantations, nursery stock ...) are normally categorically excluded under 21 CFR 25.31(a) and/or 21 CFR 25.31(c).

i. Claims of Categorical Exclusion

To claim a categorical exclusion, the applicant must state 1) that the action requested qualifies for a categorical exclusion, citing the particular categorical exclusion that is claimed, and 2) that to the applicant's knowledge, no extraordinary circumstances exist (see 21 CFR 25.15(d)).

Typically, the following statement is provided:

Applicant's name claims that approval of this (A)NDA qualifies for a categorical exclusion in accordance with 21 CFR 25.31(x) and that, to the best of the applicant's knowledge, no extraordinary circumstances exist which may significantly affect the quality of the human environment.

To facilitate Center review, when submitting a claim of categorical exclusion for actions where the drug or biologic product is derived from cultivated plants, CDER requests that the applicant provide the following information with the claim, or specifically identify where the information can be located (e.g., DMF, page number of application):

- (1) biological identification (i.e., common names, synonyms, variety, species, genus and family);
- (2) a statement as to whether wild or cultivated specimens are used;
- (3) the geographic region (e.g., country, state, province) where the biomass is obtained; and
- (4) a statement indicating:
 - (a) whether the species is determined under the Endangered Species Act (ESA) or the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) to be endangered or threatened,
 - (b) whether the species is entitled to special protection under some other Federal law or international treaty to which the United States is a party

- (c) whether the species is the critical habitat of another species that has been determined to be endangered or threatened under ESA or CITES
- (d) whether the species is the critical habitat of another species entitled to special protection under some other Federal law or international treaty to which the United States is a party.

CDER will use this information to evaluate whether the claim of categorical exclusion is appropriate.

b. Non-Cultivated Plants

An Environmental Assessment (EA) is ordinarily required for NDAs, abbreviated applications and applications for marketing approval of a biologic product where the drug or biologic product is *derived from plants taken from the wild*. EAs are also ordinarily required for supplements to such applications that relate to changes in the source of the wild biomass (e.g., species, geographic region where biomass is obtained), or supplements to such applications that are considered to increase the use of an active moiety or biologic substance and which will cause more harvesting than what was described in the original EA. The content and format follows.

i. EA Content and Format

This section describes the basic information that should be submitted in an EA for a drug or biologic product derived from plants taken from the wild. Alternative formats may be used, but the applicant should recognize that use of a standard format, such as described in this guidance, promotes efficiency in the review process.

1. Date

The EA should include the date the EA was originally prepared and the date(s) of any subsequent amendments.

2. Name of Applicant or Petitioner

The EA should identify the applicant who is submitting the application.

3. Address

The EA should contain the address where all correspondence is to be directed.

4. Description of Proposed Action

- a. Requested Approval

The description of the requested approval should include the drug or biologic application number (if available), the drug or biologic product name, the dosage form and strength, and a brief description of the product packaging. For example, "XYZ Pharmaceuticals has filed an NDA pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADE NAME (established name), 250 mg and 500 mg, packaged in OHDPE bottles. An EA has been submitted pursuant to 21 CFR part 25."

b. Need for Action

The EA should briefly describe the drug's or biologic's intended uses in the diagnosis, cure, mitigation, treatment, or prevention of disease.

c. Locations of Use

The EA should identify the location(s) where the product will be used. Depending on the type of product and its use, the locations of use are typically identified as hospitals, clinics and/or patients in their homes. If use is expected to be concentrated in a particular geographic region, this fact should be included.

d. Disposal Sites

Unless other disposal methods by the end user are anticipated, it is sufficient to state that at U.S. hospitals, pharmacies, or clinics, empty or partially empty packages will be disposed of according to hospital, pharmacy, or clinic procedures and/or that in the home, empty or partially empty containers will typically be disposed of by a community's solid waste management system, which may include landfills, incineration, and recycling, although minimal quantities of the unused drug could be disposed of in the sewer system.

5. Identification of Substances that are the Subject the Proposed Action

a. Nomenclature

- i. Established Name (U.S. Adopted Name-USAN)
- ii. Brand/Proprietary Name/Tradename
- iii. Chemical Names or Genus/Species of Biologic Product
 - Chemical Abstracts (CA) Index Name (inverted form)
 - Systematic Chemical Name (uninverted form)

b. Chemical Abstracts Service (CAS) registration number

c. Molecular Formula

d. Molecular Weight

e. Structural (graphic) Formula/Amino Acid Sequence

6. Environmental Issues

a. Use of Resources

Information relating to the source of the plant, such as biological identification, government oversight of harvesting, geographic region where biomass is obtained, and harvesting methods

and techniques should be included in the EA. The EA should include, but not be limited to, the following types of information:

- Biological identification (i.e., common names, synonyms, variety, species, genus, and family).
- A statement as to whether wild or cultivated specimens are used.
- The geographic region (e.g., country, state, province) where biomass is obtained and whether harvesting occurred on public or private land.
- A brief description of government oversight of the harvesting including, if applicable, the identity of the authority permitting harvesting and identity of authorities consulted regarding the harvesting. Submission of copies of permits or harvesting regulations relating to the specific species is helpful. For species covered under CITES, CDER or CBER could request copies of relevant permits.
- A brief description of the applicant's oversight of the harvesting.
- A statement indicating:
 - (a) whether the species is determined under the Endangered Species Act (ESA) or the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) to be endangered or threatened,
 - (b) whether the species is entitled to special protection under some other Federal law or international treaty to which the United States is a party
 - (c) whether the species is the critical habitat of another species that has been determined to be endangered or threatened under ESA or CITES
 - (d) whether the species is the critical habitat of another species entitled to special protection under some other Federal law or international treaty to which the United States is a party.
- A statement describing the part of the plant used and whether it is a renewable resource.
- A detailed description of the method of harvest including such information as the type of harvesting (e.g., clear cut, gleaning from timber stands destined for clear cutting, salvaging, pruning), frequency of harvest, whether the harvesting technique will affect the ecosystem (and if so, how), and whether the harvesting is conducted in accordance with government regulations or guidance (include citations to applicable regulations or guidance).
- Bulk weight or other appropriate measure of biomass needed to yield one kilogram of active moiety or biologic substance, the amount that has been harvested to date to support the proposed Agency action for the product, and the amount expected to be harvested in the future.
- The amount of biomass needed to produce the active moiety or biological substance used to treat the average patient. This should be provided in terms easy to understand (e.g., 2-3 trees per patient). The expected patient population and number of kilograms of active moiety or biologic substance needed per year should be provided. (*This information may be provided in confidential appendix*).
- An estimate of the total number of plants in the geographic region where the biomass is obtained.
- Any uses of the plant other than for the proposed use (humans, food source, habitat for fauna).

- Plant growth rates and/or life span and, if applicable, the rate of reproduction/regeneration.
- A discussion of whether harvesting provides for sustained yield (e.g., percentage of sustainable harvest needed to supply annual needs based on the proposed use and any prior approved uses).

7. Mitigation Measures

Describe measures taken to avoid or mitigate any potential adverse environmental effects associated with the proposed action. If no adverse environmental effects have been identified, it should be so stated and indicated that no mitigation measures are needed.

Discuss mitigation measures for actions involving flora such as mitigation measures taken before (e.g., developing a process that uses a renewable part of a plant), during (e.g., limiting/selecting specimens to be harvested), and after harvesting (e.g., reforestation) (see 40 CFR 1508.20).

8. Alternatives to the Proposed Action

If no potential adverse environmental effects have been identified for the proposed action, the EA should state this. If potential adverse environmental effects have been identified for the proposed action, the EA "shall discuss any reasonable alternative course of action that offers less environmental risk or that is environmentally preferable to the proposed actions" (21 CFR 25.40(a)). The discussion should include the no-action alternative and measures that FDA or another government agency could undertake as well as those the applicant or petitioner would undertake. The EA should include a description of those alternatives that will enhance the quality of the environment and avoid some or all of the adverse environmental effects of the proposed action. The environmental benefits and risks of the proposed action and the environmental benefits and risks of each alternative should be discussed.

Discuss alternatives for actions involving flora. A discussion must be provided of the reasonable alternatives that were considered when deciding which biomass source would be used to produce the active moiety or biologic substance (21 CFR 25.40(a)). All alternatives that were considered (e.g., other species, wild or cultivated sources, chemical synthesis) should be discussed. A brief discussion of the factors (e.g., environmental effects) that were considered in deciding whether or not the alternative would be used should be provided. The no-action (i.e., no approval) alternative should also be discussed. It should be indicated if any of the alternatives not currently used are planned for use in the future.

9. Certification

{Applicant Name} confirms that it and the other parties with which it contracts for this harvesting (e.g., any and all buyers and collectors) have complied with all requirements under *{Country/State where harvested}* law to date relating to the harvesting of *{plant species}* for *{Applicant Name}*. *{Applicant Name}* commits that it will continue to comply with all requirements under *{Country/State where harvested}* law relating to such harvesting, including

any additional requirements that may be imposed in the future, and will take appropriate measures to ensure that all such other parties continue to comply as well.

10. List of Preparers

The EA should include the name, job title, and qualifications (e.g., educational degrees) of those persons preparing the assessment and should identify any persons or agencies consulted. Contract testing laboratories should be included in the list of consultants, although this may be included in a confidential appendix. Curriculum vitae can be included in lieu of a description of an individual's qualifications.

11. References

The EA should include a list of citations for all referenced material and standard test methods used in generating data in support of the EA. Copies of referenced articles that are not generally available and that are used to support specific claims in the EA document should be attached in a nonconfidential appendix.

12. Appendices

Both confidential and nonconfidential appendices can be included. A list of the appendices should be included in the EA summary document with a designation of confidential or nonconfidential following each of the listings. Typically, the nonconfidential appendices include data summary tables and copies of referenced articles that are generally unavailable or that were used to support specific claims in the EA. Proprietary or confidential information, such as use estimates and test reports, should be included in the confidential appendices.

EA FORMAT OUTLINE

- 1. Date**
- 2. Name of Applicant/Petitioner**
- 3. Address**
- 4. Description of Proposed Action**
 - a. Requested Approval**
 - b. Need for Action**
 - c. Locations of Use**
 - d. Disposal Sites**
- 5. Identification of Substances that are the Subject of the Proposed Action**
 - a. Nomenclature**
 - i. Established Name (U.S. Adopted Name - USAN)**
 - ii. Brand/Proprietary Name/Tradenname**
 - iii. Chemical Names or Genus/Species of Biologic Product (e.g., virus)**
 - **Chemical Abstracts (CA) Index Name**
 - **Systematic Chemical Name**
 - b. Chemical Abstracts Service (CAS) Registration Number**
 - c. Molecular Formula**
 - d. Molecular Weight**
 - e. Structural (graphic) Formula/Amino Acid Sequence**
- 6. Environmental Issues**
- 7. Mitigation Measures**
- 8. Alternatives to the Proposed Action**
- 9. List of Preparers**
- 10. References**
- 11. Appendices**
- 12. Certification**

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/s/

JEWELL D MARTIN
03/13/2012



NDA 202497

INFORMATION REQUEST

Talon Therapeutics, Inc.
Attention: Thomas J. Tarlow
Vice President of Regulatory Affairs
2207 Bridgepointe Pky. Suite 250
San Mateo, CA 94404

Dear Mr. Tarlow:

Please refer to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Marqibo® (Vincristine Liposomal Injection) 0.16 mg/mL.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your application.

1. At least 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.
2. The proposed acceptance criteria for the IVR assay appear adequate. 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	

3. Regarding your analytical methods:

(b) (4)

If you have questions, call Jewell Martin, Regulatory Project Manager, at (301) 301-2072.

Sincerely,

{See appended electronic signature page}

Sarah C. Pope Miksinski, Ph.D.
Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

LIANG ZHOU on behalf of SARAH P MIKSINSKI
03/09/2012
for BC, Saah

Baird, Amy

From: Baird, Amy
Sent: Friday, March 02, 2012 10:48 AM
To: 'Tom Tarlow'
Subject: RE: NDA 202497 Marqibo - FDA Clinical Request

Tom,

Thank you for the email below. However, it did not provide clarification to the questions. Please attempt to provide a response via email today.

For subject ID 0026- 0391

Please clarify whether this subject had kidney biopsy (not imaging) on (b) (6) at screening visit. CRF13 (page 37 of 295) reports "kidney biopsy: recurrent ALL infiltrate".

With respect to bone marrow evaluation and laboratory tests, please see below:

(b) (6) - Course 1 Day 28: BMBx = M1, ANC = 1000, PLT = 96,000 → CRp

(b) (6) - Course 2 Day 15: BMBx = M1

(b) (6) - Course 2 Day 28: no BMBx, ANC = 500, PLT = 103,000 → CRi

(b) (6) - Course 3 Day 15: BMBx = M1

(b) (6) - Course 3 Day 28 (or Course 4 Day1): no BMBx, ANC = 900, PLT = 139,000 → CRp

(b) (6) (End of Therapy): BMBx = M1, no CBC on 8/05/2008

(b) (6) Conditioning chemotherapies for HSCT

(b) (6): ANC = 3700 and PLT = 3000

Is there a CBC for this subject at the End of Therapy and before conditioning regimen of HSCT? Please provide the result.

You reported Course 3 Day 28 as CR. ANC is less than 1000 on Course 4 Day 1. The last PLT (after HSCT) is only 3000. Please provide clarification on reported CR.

For subject ID 0193-0694

Please provide evidence (CBC or BMBx) based on which relapse was declared on (b) (6).

Please do not hesitate to contact me should you have any questions.

Amy Baird

Regulatory Project Manager

Division of Hematology Products, CDER, FDA

10903 New Hampshire Ave

WO #22, Room 1223

Silver Spring, MD 20993

Telephone: 301-796-4969

Facsimile: 301-796-9845

Email: amy.baird@fda.hhs.gov

From: Tom Tarlow [mailto:TTarlow@Talontx.com]
Sent: Thursday, March 01, 2012 1:08 PM
To: Baird, Amy
Subject: RE: NDA 202497 Marqibo - FDA Clinical Request

Hello Amy

Please find the Talon response to Question 1 and the Question 2 below. Earlier I had told you that we would not have the data tables with BM and CBC counts however these were provided to me for submission to you. Let me know whether your team wants these data submitted to the NDA as a formal serial.

First email received on 2/29/12

Talon Response to Question 1:

We have corroborated the Agency assertion that for HBS407 subject 0193-0694 there are differing relapse dates ((b) (6)) for the Data Listing and the CRF pages, respectively. Talon used the (b) (6) date from the Data Listing for the calculation of the response duration for this subject. We believe that taking the most conservative date for an estimate of relapse for this subject is appropriate. We continue to investigate the apparent discrepancy between the CRF pages and the Data Listing.

Talon Response to Question 2:

The following is Talon's view of the clinical picture for HBS407 subject 0026-0391. For this subject, there was an apparent enlargement of the kidney in one screening assessment that additional studies established as not extramedullary disease (EMD). The original studies could not establish a focal mass that permitted measurement and continuing assessment of this alleged organ enlargement. Also this subject had prior transplantation procedure and GVHD which may have contributed to the alleged organ enlargement. These diffuse signs resolved during treatment of this subject. It is Talon's position that the evidence does not support a clear EMD diagnosis in this subject and the PI concurs with this assessment. The data listing and the tabular summary that were requested as the second part of this question are attached.

All best
Tom

From: Baird, Amy [mailto:Amy.Baird@fda.hhs.gov]
Sent: Wednesday, February 29, 2012 7:51 AM
To: Tom Tarlow
Subject: NDA 202497 Marqibo - FDA Clinical Request

Tom,

Please refer to the NDA application for NDA 202497 Marqibo (Vincristine Sulfate Liposomes Injection) dated July 12, 2011, which provides for the proposed indication "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."

Per the request of the FDA clinical review team, provide a response to the following request by 12:00pm EST March 1, 2012.

Provide further information and clarification regarding the following subjects:

1) Subject 0193-0694: You reported relapse date of (b) (6) Data Listing. However, CRF for this subject

shows bone marrow evaluation and labs on [REDACTED] ^{(b) (6)} indicating CR. Please explain.

2) Subject 0026-0391: 1) Please provide the status of extramedullary disease in this subject. CRF and data listing contain discordant and non-clear information. 2) Please also in a table provide the results of all bone marrow and CBC evaluations with corresponding dates of performance for this subject."

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird

Regulatory Project Manager

Division of Hematology Products, CDER, FDA

10903 New Hampshire Ave

WO #22, Room 1223

Silver Spring, MD 20993

Telephone: 301-796-4969

Facsimile: 301-796-9845

Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
03/02/2012

Baird, Amy

From: Baird, Amy
Sent: Wednesday, February 29, 2012 4:40 PM
To: 'Tom Tarlow'
Subject: NDA 202497 Marqibo - FDA Clinical Request for Information

Tom,

Please refer to the NDA application for NDA 202497 Marqibo (Vincristine Sulfate Liposomes Injection) dated July 12, 2011, which provides for the proposed indication "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."

Per the request of the FDA clinical review team, provide a response to the following request by 12:00pm EST March 1, 2012.

In your HBS407 study report Table 14.1.8.2 and dataset PX, 36 patients received asparaginase products before enrolling to the study. However, according to your patient data listing 16.2.1.10, 43 patients had asparaginase prior to the study. Please explain this discrepancy.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
02/29/2012

Baird, Amy

From: Baird, Amy
Sent: Wednesday, February 29, 2012 10:51 AM
To: 'Tom Tarlow'
Subject: NDA 202497 Marqibo - FDA Clinical Request

Tom,

Please refer to the NDA application for NDA 202497 Marqibo (Vincristine Sulfate Liposomes Injection) dated July 12, 2011, which provides for the proposed indication "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."

Per the request of the FDA clinical review team, provide a response to the following request by 12:00pm EST March 1, 2012.

Provide further information and clarification regarding the following subjects:

- 1) Subject 0193-0694: You reported relapse date of [REDACTED] (b) (6) Data Listing. However, CRF for this subject shows bone marrow evaluation and labs on [REDACTED] (b) (6) indicating CR. Please explain.
- 2) Subject 0026-0391: 1) Please provide the status of extramedullary disease in this subject. CRF and data listing contain discordant and non-clear information. 2) Please also in a table provide the results of all bone marrow and CBC evaluations with corresponding dates of performance for this subject."

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
02/29/2012

Baird, Amy

From: Baird, Amy
Sent: Wednesday, February 22, 2012 10:39 AM
To: 'Tom Tarlow'
Subject: NDA 202497 Marqibo - FDA Clinical Request

Tom,

Please refer to the NDA application for NDA 202497 Marqibo (Vincristine Sulfate Liposomes Injection) dated July 12, 2011, which provides for the proposed indication "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."

Per the request of the FDA clinical review team, provide a response to the following request by COB today, February 22, 2012.

Please update the status of your confirmatory Study TTX404. Please provide the following information: How many patients to date have been enrolled in the Study TTX404 and to which sites? How many active sites are open to date for enrollment into Study TTX404? What is the estimated time of completion for Study TTX404?

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
02/22/2012

Baird, Amy

From: Baird, Amy
Sent: Thursday, February 09, 2012 11:11 AM
To: 'Tom Tarlow'
Subject: NDA 202497 Marqibo - FDA Clinical and Microbiology Requests

Please refer to the NDA application for NDA 202497 Marqibo (Vincristine Sulfate Liposomes Injection) dated July 12, 2011, which provides for the proposed indication "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."

Per the request of the FDA Clinical and Microbiology review teams, please provide a response to the following questions NLT Wednesday, February 15, 2012.

Clinical

For subject 0193-0692 you reported CR as First and Final IRRC Response (Listing 16.2.3.4.1). However, there are discrepancies in this subject's CRFs related to Course 1 Day 28. Initially an agreement between central and local pathologists on M1 marrow was reported, however, this case was also read by an adjudicator as M2 (i.e. no CR), which indicates discordance between local and central pathologists. There is also a report under Course 4 Day 28 section, which according to the dates should have been under Course 1 Day 28. This reports states "Treatment Schedule 1" and the dates of local, central and adjudicator pathology reports are corresponding to Course 1. In this report Central and Adjudicator agreed on non-M1 (i.e. no CR) result.

Additionally, according to CRFs, the results of bone marrow aspirate and biopsy examinations on Course 2 Day 28, Course 3 Day 28 and Course 4 Day 28 showed consistently greater than 5% blasts in the bone marrow by central pathologist, which indicates no CR.

Please clearly explain the above discrepancies. Because of consistently greater than 5% blasts in the bone marrow, this subject cannot be considered as a CR.

Microbiology

1. For the constitution of the Marquibo kit, the contents of three separate sterile vials will be combined in the VSLI vial, heated at 65 + 2oC in a water bath for the eventual administration of the admixture with 5% Dextrose Injection or 0.9% Sodium Chloride Injection. What precautions will be taken to ensure that aseptic conditions will be maintained throughout the constitution process, in a pharmacy setting.
2. The current label requires the constituted product to be used within 12 hours of constitution start time. Microbiological studies in support of the 12-hour post-constitution storage time (as stated in the proposed labeling) have not been provided. Please provide a risk assessment summarizing studies that show adventitious microbial contamination does not grow under the storage conditions. Reference is made to Guidance for Industry: ICH Q8 Pharmaceutical Development, Section II.E and Guidance for Industry: ICH Q1A(R2) Stability Testing of New Drug Substances and Products, Section 2.2.7.
<http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html>.

Generally, "no growth" is interpreted as not more than a 0.5 log₁₀ increase from the initial count; however other evidence of growth may be significant. The test should be run at the label's recommended storage conditions, be conducted for 2 to 3-times the label's recommended storage period, and use the label-recommended fluids inoculated with low numbers (<100 CFU/mL) of challenge microbes. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections. In lieu of these data, the product labeling should recommend that the postconstitution storage period is not more than 4 hours at room temperature.

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird

Regulatory Project Manager

Division of Hematology Products, CDER, FDA

10903 New Hampshire Ave

WO #22, Room 1223

Silver Spring, MD 20993

Telephone: 301-796-4969

Facsimile: 301-796-9845

Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
02/09/2012

Baird, Amy

From: Baird, Amy
Sent: Friday, January 20, 2012 6:03 PM
To: 'Tom Tarlow'
Subject: NDA 202497 Marqibo - FDA Clinical Request

Please refer to the NDA application for NDA 202497 Marqibo (Vincristine Sulfate Liposomes Injection) dated July 12, 2011, which provides for the proposed indication "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."

Per the request of the FDA clinical review team, please provide a response to the following questions NLT Tuesday, January 24, 12:00pm.

In Study HBS407, the following concomitant corticosteroid use was reported by you (including taper off of systemic steroid medications by Cycle 1 Day 5): dexamethasone, 21.5%; prednisone, 20.0%; hydrocortisone, 21.5%; methylprednisolone sodium succinate, 12.3%; hydrocortisone sodium succinate, 9.2%; methylprednisolone, 6.2%; prednisolone acetate, 1.5%; dexamethasone sodium phosphate, 1.5%; prednisolone, 1.5% (source: ISS Tables, Table 1.8.1).

- 1) How many of the concomitant corticosteroids were tapered before Cycle 1 day5? How many continued during the study? Please provide the information in a Table with Subject's ID.
- 2) If a steroid was continued beyond day 5, please provide the route of administration as well as frequency and duration of administration for each corticosteroid.

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
01/20/2012



NDA 202497

INFORMATION REQUEST

Talon Therapeutics, Inc
Attention: Thomas J Tarlow, Vice President
Regulatory Affairs and Quality Assurance
2207 Bridgepointe Parkway, Suite 250
San Mateo, CA 94404

Dear Mr. Tarlow:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Marqibo® (Vincristine Sulfate Liposomes Injection) 0.16 mg/mL

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

DRUG SUBSTANCE:

[Redacted] (b) (4)

DRUG PRODUCT:

For VSI

Provide full comparative data for the complete impurity profiles of the proposed VSI formulation and the reference listed drug.

Under accelerated conditions, OOS results were observed at 3 and 6 months [Redacted] (b) (4)

[Redacted]

Assay results were also observed to be OOS at 6 months under accelerated conditions. As per ICH Q1A guidelines, address the effect of short-term excursions outside the labeled storage conditions (e.g., during shipment and handling) since significant changes (OOS results) are noted within the first 3 months of testing at the accelerated storage condition.

[Redacted] (b) (4)
Conduct this study again to assess the effect of freeze-thaw on the VLS drug product.

For SCLI

Particle size distribution of the liposome is considered a critical quality attribute since it affects the performance of the product. Tighten the acceptance limit for particle size distribution based on historical batch data, [REDACTED] (b) (4)

[REDACTED]

[REDACTED] (b) (4)

Propose an acceptance criterion for individual unspecified degradation products for SCLI based on historical batch analysis data.

For Marqibo kit

For the specification for the Marqibo Kit, [REDACTED] (b) (4)

[REDACTED]

Propose a sufficiently specific test method or use a combination of two complementary methods to confirm the identity of the drug substance per ICH Q6A guidelines.

Tighten the acceptance limit for particle size distribution based on historical batch data [REDACTED] (b) (4)

[REDACTED]).

If you have any questions, call Scott N. Goldie, Ph.D., Sr. Regulatory Health Project Manager for Product Quality, at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Sarah C. Pope Miksinski, Ph.D.
Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

SARAH P MIKSINSKI
01/09/2012



NDA 202497

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Talon Therapeutics, Inc.
2207 Bridgepointe Parkway
Suite 250
San Mateo, California 94404

ATTENTION: Thomas J. Tarlow
Vice President, Regulatory Affairs and Quality Assurance

Dear Mr. Tarlow:

Please refer to your New Drug Application (NDA) dated July 12, 2011, received July 12, 2011, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Vincristine Sulfate Liposome Injection, 0.16 mg/mL.

We also refer to your September 20, 2011, correspondence, received September 20, 2011, requesting review of your proposed proprietary name, Marqibo. We have completed our review of Marqibo and have concluded that it is acceptable.

Marqibo will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If any of the proposed product characteristics as stated in your September 20, 2011, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sue Kang, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4216. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Amy Baird at (301) 796-4969.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
12/15/2011

Baird, Amy

From: Baird, Amy
Sent: Wednesday, December 14, 2011 11:01 AM
To: 'Tom Tarlow'
Subject: NDA 202497 Marqibo - DMEPA Request for Information

Please refer to the NDA application for NDA 202497 Marqibo (Vincristine Sulfate Liposomes Injection) dated July 12, 2011, which provides for the proposed indication "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."

Per the request of the FDA Division of Medication Error Prevention and Analysis, please provide address the following comments as soon as possible:

The design of Marqibo introduces opportunities for the occurrence of medication errors in many steps of the medication use process. We recommend that the following issues be addressed in a submission to the NDA.

1. Procurement of medication:

Errors may occur in the procurement phase when the product is order using the established name (Vincristine Sulfate Liposomes Injection vs. Vincristine Sulfate Injection). We acknowledge the fact that you propose to revise the carton labeling to [REDACTED] (b) (4) as well as the description of the contents of the kit. However, at this time, we continue to be concerned regarding the potential for this confusion.

2. Prescribing:

Medication errors may occur when prescribers write a prescription using the established name, "Vincristine injection" or "Vincristine." Practitioners will not know which product to dispense the currently marketed Vincristine sulfate products or the proposed Vincristine Sulfate Liposomes Injection. Moreover, the proposed dose of Marqibo is 50% more Vincristine than the dose for the marketed Vincristine products (1.4 mg/m² vs. 2.25 mg/m²). Furthermore, a single dose of Vincristine is often capped to a maximum dose of 2 mg. Thus, an overdose of vincristine may be more than 50% should these products be confused during prescribing as there is no maximum dose on the proposed product. We note you consider the difference in dosing as a source of differentiation between these products. However, this noted difference in dose does not address our concern because the introduction of liposomal formulations of medications with differing doses have resulted in medications errors. For example, post marketing experience with conventional Amphotericin B and Amphotericin B liposomal formulation, which also differ in dose, demonstrates medication errors in which patients have received either an overdose or under dose of medication due to confusion between the products and their respective dosing. Many of these errors involve the use of the established name in the medication use process, including one case in which the established name was used when prescribing. These errors have resulted in patients experiencing sepsis, cardiac arrest, and even death.

3. Preparation and Dispensing:

We remain concerned with the packaging configuration and the complexity of the preparation of the product:

- The product preparation includes [REDACTED] (b) (4) steps which provides for multiple opportunities for errors.
- Three separate vials are required to achieve the final product. In addition, the vials must be combined in a specific order and heated at a specified temperature (65°C) and for a specific time period (10 minutes). We are concerned about the safety of the product if prepared outside of these parameters and dosing errors that may arise due to the multiple vial preparation requirement.
- There are a number of required materials for the proposed product preparation. If the required materials are not supplied in the kit (i.e., water bath, calibrated thermometer, calibrated electronic timer, sterile syringes, sterile venting filter needles), this may lead to pharmacy personnel using alternative means to prepare the product which may lead to confusion, error, and the possibility that the product is not properly prepared for patient administration. We recognize this is a designated orphan drug which limits this medication's use, but this limited use may increase the likelihood a pharmacy may not have the necessary equipment to compound this product.
- You propose to summarize the current experience with Marqibo in the investigational setting. We request you include all constitution or preparation issues that arose during the clinical trials of this medication in this summary.

• You note Marqibo contains a “comprehensive and historically valid set of directions for pharmacy-based constitution” and propose to provide (b) (4). However, the proposed complex constitution process is not considered usual practice within inpatient pharmacies. We recommend that you conduct a Human Factors assessment of the constitution procedure and submit these findings to the NDA to demonstrate the safe preparation of this product.

• (b) (4). In addition, the 5 mg/5 mL vial presentation of Vincristine Sulfate injection was marketed in the US in the past. Furthermore, the currently US marketed Vincristine Sulfate Injection is also a liquid formulation. Thus, practitioners may believe that the vincristine sulfate injection vial included in the kit is ready for administration and requires no further dilution. You propose to label the vial of vincristine sulfate injection contained in the kit with a description the Vincristine Sulfate vial is for the further use in the preparation of Marqibo. However, this warning on the container label may not adequately address this risk.

• We note you compare the use of Marqibo to Myocet, a liposomal formulation of Doxorubicin approved in the European Union, as a precedent for DMEPA’s prior safety concerns regarding the preparation of this product. However, we have no data demonstrating successful use in the EU. In addition, the practice of pharmacy in hospitals in the EU differs to practice in the United States and thus offers different failures in the medication use system that must be considered to ensure the safe use of the product.

4. Administration:

Infusions for Vincristine sulfate are administered over 10 to 15 minutes while Marqibo is recommended to infuse over 60 minutes. Vincristine sulfate is considered a high alert medication for most healthcare system across the countries due to associated fatal medication errors. Medication errors may occur in instances where nurses familiar with infusing marketed vincristine may infuse Marqibo too fast (over 15 minutes).

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
12/14/2011



NDA 202497

**METHODS VALIDATION
MATERIALS RECEIVED**

Talon Therapeutics, Inc.
Attention: Thomas Tarlow
VP, Regulatory Affairs and Quality Assurance
2207 Bridgepointe Parkway
Suite 250
San Mateo, CA 94404

Dear Mr. Thomas Tarlow:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Marqibo (Vincristine Sulfate Liposomes Injection), 0.16 mg/mL and to our 09/27/2011, letter requesting sample materials for methods validation testing.

We acknowledge receipt on 10/18/2011 and 11/02/2011, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (James.Allgire@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

James F. Allgire
Team Leader
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

JAMES F ALLGIRE
11/21/2011

Baird, Amy

From: Baird, Amy
Sent: Wednesday, November 16, 2011 1:27 PM
To: 'Tom Tarlow'
Subject: NDA 202497 Marqibo - FDA Clinical Request for Information

Please refer to the NDA application for NDA 202497 Marqibo (Vincristine Sulfate Liposomes Injection) dated July 12, 2011, which provides for the proposed indication "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."

Per the request of the FDA Clinical Review Team, please provide the following:

- 1) In Study HBS407, Twelve (12) patients underwent stem cell transplantation after administration of Marqibo. Please provide a Table that summarizes the reasons for which the rest of the 53 patients were unable to undergo stem cell transplant.
- 2) Seven of the 12 patients who underwent stem cell transplant did not achieve CR or CRi after Marqibo. Please provide a Table that summarizes all subsequent anti-leukemic therapies after Marqibo and before Transplant excluding transplant conditioning regimens.
- 3) In the NDA 202497, Study HSB407, for a few patients date of deaths were not reported. Please provide survival update for those patients.

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
11/16/2011

Baird, Amy

From: Baird, Amy
Sent: Monday, October 17, 2011 1:17 PM
To: 'Tom Tarlow'
Subject: NDA 202497 Marqibo - Request from OSE

Tom,

Please refer to the NDA application for NDA 202497 Marqibo (Vincristine Sulfate Liposomes Injection) dated July 12, 2011, which provides for the proposed indication "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."

Per the request of the FDA Office of Surveillance and Epidemiology, please provide a Word copy of the Medication Guide.

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
10/17/2011



NDA 202-497

INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Talon Therapeutics, Inc.
Attention: Thomas Tarlow
VP, Regulatory Affairs and Quality Assurance
2207 Bridgepointe Parkway, Suite 250
San Mateo, CA 94404

Dear Mr. Thomas Tarlow:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Marqibo (Vincristine Sulfate Liposomes Injection), 0.16 mg/mL.

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by Cetero Research in Houston, Texas (Cetero).¹ The pervasiveness and egregious nature of the violative practices by Cetero has led FDA to have significant concerns that the bioanalytical data generated at Cetero from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or “prep” run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or “prep” runs that prevented Cetero and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by Cetero Research in Houston, Texas during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is

¹ These violations include studies conducted by Bioassay Laboratories and BA Research International specific to the Houston, Texas facility.

searching available documentation to determine which NDAs are impacted by the above findings.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by Cetero Research in Houston, Texas during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have any questions, call Amy Baird, Regulatory Project Manager, at (301) 796-4969.

Sincerely,

{ See appended electronic signature page }

Rafel Dwaine Rieves, M.D
Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

KYONG A KANG
10/12/2011
Signing for Rafael Rieves

Baird, Amy

From: Baird, Amy
Sent: Wednesday, October 05, 2011 2:34 PM
To: 'Tom Tarlow'
Subject: NDA 202497 Marqibo - FDA Request for Clinical Information

Tom,

Please refer to the NDA application for NDA 202497 Marqibo (Vincristine Sulfate Liposomes Injection) dated July 12, 2011, which provides for the proposed indication "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."

Per the request of the FDA clinical review team, please provide the following information:

Provide patient data listings for your efficacy response in Study protocol HBS407, by clinical study site. Specifically, provide specific study subject values for the following: bone marrow (e.g., M:E ratio, blasts % values), and corresponding peripheral blood findings (e.g., platelet and granulocyte counts).

Please provide a response to these requests NLT October 13, 2011.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
10/05/2011



NDA 202497

**REQUEST FOR METHODS
VALIDATION MATERIALS**

Talon Therapeutics, Inc.
Attention: Thomas Tarlow
VP, Regulatory Affairs and Quality Assurance
2207 Bridgepointe Parkway
Suite 250
San Mateo, CA 94404

Dear Mr. Thomas Tarlow:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Marqibo (Vincristine Sulfate Liposomes Injection), 0.16 mg/mL.

We will be performing methods validation studies on Marqibo (Vincristine Sulfate Liposomes Injection), 0.16 mg/mL, as described in NDA 202497.

In order to perform the necessary testing, we request the following sample materials and equipments:

3- Marqibo kits.

(b) (4)

Include the MSDSs and certificates of analysis standard kits and chemicals.
Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: James F. Allgire

1114 Market Street, Room 1002
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (James.Allgire@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

James F. Allgire
Team Leader
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

JAMES F ALLGIRE
09/27/2011



NDA 202497

FILING COMMUNICATION

Talon Therapeutics Incorporated
Attention: Thomas J. Tarlow
Vice President, Regulatory Affairs
2207 Bridgepointe Parkway, Suite 250
San Mateo, CA 94404

Dear Mr. Tarlow:

Please refer to your New Drug Application (NDA) dated July 12, 2011, received July 12, 2011, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Marqibo (vincristine sulfate liposomal injection).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is May 13, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by April 23, 2012.

During our filing review of your application, we identified the following potential review issues:

ONDQA Biopharmaceutics

1. At least 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.
2. 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.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

The Full Prescribing Information section of the labeling is incorrectly formatted into 2 columns. Only the Highlights and Table of Contents should be in a column format.

We request that you resubmit labeling that addresses this issue by October 14, 2011. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

We will review this application under the provisions of 21 CFR 314 Subpart H – *Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses*. Unless we otherwise inform you, as required by 21 CFR 314.550, you must submit during the preapproval review period copies of all promotional materials, including promotional labeling and advertisements, intended for dissemination or publication within 120 days following marketing approval (i.e., your launch campaign). We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and proposed package insert (PI)/Medication Guide/patient PI (as applicable). Send each submission directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications (DDMAC)
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call DDMAC at 301-796-1200.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Amy Baird, Regulatory Project Manager, at (301) 796-4969.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, M.D.
Acting Director
Division of Hematology Products
Office of Hematology Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

ANN T FARRELL
09/23/2011

Baird, Amy

From: Baird, Amy
Sent: Wednesday, September 21, 2011 11:10 AM
To: 'Tom Tarlow'
Subject: NDA 202497 Marqibo - Scheduled Telecom

Tom,

Per Talon's request, we have scheduled a telecom to discuss NDA 202497 Marqibo. Below is the date and time of the telecom. Please let me know if the proposed time is convenient for yourself and your colleagues.

October 6, 2011
12:30pm-1:00pm

FDA Attendees

Ann Farrell, M.D., Acting Director, Division of Hematology Products (DHP)
Edvardas Kaminskas, M.D., Acting Deputy Director, DHP
Qin Ryan, M.D., Ph.D., Clinical Team Leader, DHP
Ashkan Emadi, M.D., Clinical Reviewer, DHP
Janice Brown, Ph.D., Pharmaceutical Assessment Lead, ONDQA
Xiao Hong Chen, Ph.D., Chemistry Reviewer, ONDQA
Haleh Saber, Ph.D., Supervisory Pharmacologist, DHP
Yanli Ouyang, Ph.D., Pharmacology Reviewer, DHP
Mark Rothmann, Ph.D., Biometrics Team Leader, DB5
Lan Huang, Ph.D., Biometrics Reviewer, DB5
Julie Bullock, Ph.D., Clinical Pharmacology Team Leader, DCP5
Bahru Habtemariam, Ph.D., Clinical Pharmacology Reviewer, DCP5
Amy Baird, Regulatory Project Manager, DHP

Please provide an agenda for the telecom by COB September 28, 2011.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
09/21/2011

Baird, Amy

From: Baird, Amy
Sent: Thursday, September 01, 2011 2:38 PM
To: 'Tom Tarlow'
Cc: (b) (4)
Subject: RE: Marqibo PLR-compliant label submission

Tom,

Your proposal in the paragraph below is acceptable with the FDA review team.

We propose to maintain the same annotated label containing hyperlinks to various sections of the NDA that support label counterpart sections.

Our justification is that we believe there is the potential to create needless error in such a formatting only revision. Each hyperlink would have to be broken and re-created. It could delay ongoing reviews of the NDA. Since the label revision was only for PLR formatting, no new content was introduced, therefore no new hyperlinks are needed or appropriate for the annotated label currently in the NDA. Additionally, the Highlights' area of the PLR formatted label is drawn entirely from the body of the label, therefore the current hyperlinks should and must cover information presented in the 'Highlights' section. Please let me know if a revised version of the annotated label is required for a filing decision.

Amy Baird

Regulatory Project Manager

Division of Hematology Products, CDER, FDA

10903 New Hampshire Ave

WO #22, Room 1223

Silver Spring, MD 20993

Telephone: 301-796-4969

Facsimile: 301-796-9845

Email: amy.baird@fda.hhs.gov

From: Tom Tarlow [mailto:TTarlow@Talontx.com]
Sent: Wednesday, August 31, 2011 10:15 PM
To: Baird, Amy
Cc: (b) (4)
Subject: Marqibo PLR-compliant label submission
Importance: High

Hello Amy

The revised Marqibo PLR-compliant label is QC'd and final. The revisions to the label were only in regard to the PLR format. There were no content-related revisions to the revised Marqibo PLR-compliant label. We have forwarded the document to our contract e-publisher who is copied on this email. They, in turn, will transfer the revised Marqibo PLR-compliant label to the team that creates SPL version for re-submission to the NDA.

We plan to replace 3 files in M1. The revised Marqibo PLR-compliant label in SPL format will be inserted in the

spl folder to replace the current version. Additionally, 2 files, one Word and one pdf entitled 'draft-label-text' will be replaced with revised Marqibo PLR-compliant label versions. Will you accept the revised Marqibo PLR-compliant label delivered initially via email as an informal replacement followed by the revised files in a sequence submission, '0001', to the eCTD to replace the original files? The sequence submission, '0001' will arrive at FDA by September 6, 2011. The files will be sent to you via email by September 2, 2011.

We propose to maintain the same annotated label containing hyperlinks to various sections of the NDA that support label counterpart sections.

Our justification is that we believe there is the potential to create needless error in such a formatting only revision. Each hyperlink would have to be broken and re-created. It could delay ongoing reviews of the NDA. Since the label revision was only for PLR formatting, no new content was introduced, therefore no new hyperlinks are needed or appropriate for the annotated label currently in the NDA. Additionally, the 'Highlights' area of the PLR formatted label is drawn entirely from the body of the label, therefore the current hyperlinks should and must cover information presented in the 'Highlights' section. Please let me know if a revised version of the annotated label is required for a filing decision.

The error regarding this inappropriate label format was entirely my own. I am re-committed to ensuring that you receive superior efforts and outcomes for the remainder of our review.

Sincerely

Tom

Thomas J Tarlow
Vice President
Regulatory Affairs and Quality Assurance
Talon Therapeutics, Inc (formerly Hana Biosciences)
650 228 5066 direct
650 228 5067 fax
(b) (6) cell
tom.tarlow@hanabiosciences.com

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/s/

AMY C BAIRD
09/01/2011

Baird, Amy

From: Baird, Amy
Sent: Wednesday, August 31, 2011 11:32 AM
To: 'Tom Tarlow'
Subject: NDA 202497 Marqibo - ODAC

Importance: High

Tom,

Please refer to your NDA application for NDA 202497 Marqibo (Vincristine Sulfate Liposomes Injection) dated July 12, 2011, which provides for the proposed indication "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.

I have been notified by the Office of Oncology Drug Products that your drug will be discussed at the ODAC scheduled in December 2011. The meeting will take place either December 7 or 8. The Office of Advisors and Consultants will be in contact with you soon and will provide additional details. Also, please do not disclose this information to the public until the Federal Register notice has been published.

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
08/31/2011

Baird, Amy

From: Baird, Amy
Sent: Tuesday, August 30, 2011 11:52 AM
To: 'Tom Tarlow'
Subject: NDA 202497 Marqibo - FDA Request

Please refer to your NDA application for NDA 202497 Marqibo (Vincristine Sulfate Liposomes Injection) dated July 12, 2011, which provides for the proposed indication "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."

The labeling provided with the NDA submission is in the old format. Please provide labeling that is in Structured Product Labeling format as required by the Physician's Labeling Rule as soon as possible as this is a potential filing issue.

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
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/s/

AMY C BAIRD
08/31/2011



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 059056

MEETING MINUTES

Hana Biosciences, Inc.
Attention: Thomas J. Tarlow
Vice President, Regulatory Affairs
7000 Shoreline Court
Suite 370
South San Francisco, CA 94080

Dear Mr. Tarlow:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Marqibo.

We also refer to the meeting between representatives of your firm and the FDA on April 20, 2010. The purpose of the meeting was to have a pre-NDA discussion for Marqibo in the treatment of Philadelphia Chromosome-Negative Acute Lymphoblastic Leukemia (ALL).

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Amy Baird, Regulatory Project Manager at (301) 796-4969.

Sincerely,

{See appended electronic signature page}

Amy Baird
Regulatory Project Manager
Division of Hematology Drug Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: April 20, 2010 11:00-12:00
Meeting Location: WO22, Room 1417

Application Number: IND 059056
Product Name: Marqibo
Indication: Treatment of Philadelphia chromosome-negative acute lymphoblastic leukemia (ALL) in adults in second relapse or whose disease has progressed following two treatment lines of anti-leukemia therapy

Sponsor/Applicant Name: Hana Biosciences, Inc.
Meeting Chair: Patricia Cortazar, M.D.
Meeting Recorder: Amy Baird

FDA ATTENDEES

Edvardas Kaminskas, M.D., Acting Deputy Director, DHP
Patricia Cortazar, M.D., Clinical Team Leader, DDOP
Kristen Snyder, M.D., Clinical Reviewer, DDOP
Doo Young Lee Ham, Ph.D., Pharmacology Reviewer, DDOP
Shenghui Tang, Ph.D., Statistical Team Leader, DB5
Chia-Wen Ko, Ph.D., Statistical Reviewer, DB5
Hua Lillian Zhang, Ph.D., Clinical Pharmacology Reviewer, DCP5
Melina Griffis, Director, Regulatory Affairs, DMEPA
Richard Abate, Pharmacist, DMEPA
Amy Baird, Regulatory Project Manager, DHP

SPONSOR ATTENDEES

Steven R. Ceitcher, M.D., President and Chief Executive Officer
Anne Hagey, M.D., Vice President and Chief Medical Officer
Jeffrey Silverman, Ph.D., Clinical Pharmacology/Pharmacokinetics
Thomas Tarlow, M.S., Vice President, Regulatory Affairs
Susan O'Brien, M.D., MD Anderson Cancer Center

(b) (4)

(b) (4)

1.0 BACKGROUND

Hana Biosciences plans to submit an NDA for Marqibo® based on HBS407 results, a 65 subject, open-label, single-arm trial. Eligibility for this trial included subjects with Philadelphia negative ALL in second relapse or who failed two treatment lines of anti-leukemia chemotherapy and who were not candidates for stem cell transplantation. Subjects were required to have achieved complete response to at least one prior therapy with a leukemia-free interval of \geq 90 days and have an ECOG performance rating of 0-3.

2. DISCUSSION

Question 1: Does the Agency agree that the data summarized above and in the Attachments (see Datasets Supporting Question 1) are sufficient to continue to support the Fast Track designation for Marqibo granted on August 21, 2007, and support a new drug application submission for the indication sought under the provisions of subpart H?

FDA Response to Question 1: Yes, the Agency agrees that the submission is sufficient to continue support of the Fast Track designation.

Whether study HPS407 will support a marketing approval of Marqibo for the treatment of adults with Philadelphia chromosome negative acute lymphoblastic leukemia (ALL) in second relapse or whose disease has progressed following two treatment lines of anti-leukemia therapy, will be a review issue.

Based on the preliminary study results that you submitted with the PreNDA package information, the application appears to be very weak. The response rate with Marqibo® is very small. The response duration is also short and could not be measured in all responding patients secondary to further treatment with bone marrow transplantation. Further, these results are not likely to support accelerated approval.

Discussion: The sponsor clarified that Cris were primarily CRP (5 out of 6) and only one patient had neutropenia. None of the patients needed ongoing platelet transfusions. Therefore, the response rate of 20% in this refractory population appears to be encouraging. The median response duration of 4.7 months should be contrasted to the 8 week median survival in a second salvage. The sponsor clarified that the patient population has no available therapies. The possible accelerated approval of Marqibo based on this data will be a review issue.

FDA Response to Question 1 continued: In order for you to request accelerated approval, you must document in the NDA that the responding patients in your single arm trial did not have available established therapeutic options at the time of entry. You need to affirm that all remission durations were censored at the time of administration of any non-protocol therapy. We refer you to the Onrigin ODAC discussion which highlight similar issues with your application.

Please provide the status of the Phase 3, randomized, multicenter study of Marqibo in elderly patients with de novo ALL (HBS404). We remind you that any consideration of accelerated approval is contingent upon the conduct of a confirmatory trial.

Discussion: [REDACTED] (b) (4)

FDA Response to Question 1 continued: We anticipate presenting this application at ODAC.

Question 2: Does the Agency agree that

- **The proposed primary safety analysis pool will include data from all subjects treated with at least one dose of Marqibo in studies HBS407 and VSLI-06 reflecting experience at the recommended dose in the indication sought as well as**
- **Supporting analyses including subjects analyzed on an individual study basis (see Table 36 and Table 37) except that**
- [REDACTED] (b) (4)

FDA Response to Question 2: No. We expect you to provide safety data and analyses by formulation.

Discussion: FDA agrees with the primary safety analysis pool for study HBS407 and VSLI-06. FDA agrees with the sponsor that the supporting analyses will not be pooled with a primary safety analysis because of differences in adverse event coding.

Question 2a: Hana proposes that the data submitted in the planned NDA regarding the potential for QT/QTc interval prolongation include:

- **All *in vitro* studies and all nonclinical studies regarding the potential for QT/QTc interval prolongation (results negative),**
- **One hundred one matched sets of baseline and end-of-infusion EKG analyses including time of EKG as well as time of most recent Marqibo dose administration from study HBS407 (results negative), and**

- **Three subjects with Holter-monitored EKG assessment that included full PK profiles from study HBS408 (results negative)**

Does the Agency find this proposal acceptable?

FDA Response to Question 2a: No. You must follow your proposed assessment for QT/QTc interval prolongation as submitted in protocol HSB408 and include the recommendations from the FDA QT-IRT. Specifically, you must provide a full assessment of at least 20 evaluable subjects which must include full ECG and PK assessments performed at the various time points previously specified in your consult with the QT/IRT team. ECG and PK assessments should be done at the same time points (ECGs should be collected prior to blood withdrawal to minimize variation due to autonomic tone changes). The ECGs and PK time points should be adequate to exclude immediate and delayed effects of Marqibo on the QT interval. Further, ECGs must be acquired in triplicate and be over-read by a central lab.

Discussion: FDA will follow-up with IRT regarding the sponsor's plan. FDA stated that the QTC evaluation will not be a filing or approvability issue for the application.

Question 3: Does the Agency agree that the proposed PK data are sufficient for NDA review?

FDA Response to Question 3: Your proposed PK data appears acceptable. The sufficiency of the data to support labeling will be a review issue.

In the NDA submission, submit all available PK datasets including individual concentration vs. time, and corresponding pharmacokinetic parameters as SAS transport files.

Question 4: Does the Agency agree that the proposed ISE content outlined above and the approach to presenting substantial evidence of effectiveness are adequate for review of the planned NDA?

FDA Response to Question 4: This will be determined within 60 days of submission of the completed application.

Question 5: Does the Agency agree that the proposed presentation of data is adequate to review the planned NDA?

FDA Response to Question 5: This will be determined within 60 days of submission of the completed application.

Question 5a: Does the Agency consider this study adequate for review for the purposes of the planned NDA in the indication sought?

FDA Response to Question 5a: As it is unclear in the study report how the patients were stratified to the hepatic impairment group, we cannot comment. The adequacy of the data to support hepatic impairment assessment will be a review issue.

Submit the following in the NDA for the hepatic study:

- A completed study report
- individual concentration vs. time, and corresponding pharmacokinetic parameters as SAS transport files
- individual subject demographics and other baseline characteristics
- individual subject laboratory parameters to classify the liver function
- listing of individual concomitant medications and significant non-drug therapies prior to and after start of study drug by patient
- safety dataset
- study protocol and any amendments
- Bioanalytical data and method validation

Question 6: Does the Agency agree that the content and format of Module 4 that is summarized in the noted sections and tables above as adequate to support review of the planned NDA?

FDA Response to Question 6: Nonclinical studies outlined in Sections 6.5.1, 6.5.2, and Table 31-33 appear adequate to support NDA filing. However, final determination of the acceptability of the study results is the review issue which may be only be determined after submission of the full study reports. Additional preclinical studies may be necessary depending upon the findings in clinical trials.

Question 6a: Does the Agency accept the data presented in murine Study PCR-0003 as supporting the bioequivalence of (b) (4) and 3-vial and thereby the applicability of the nonclinical program to the support of the clinical program conducted with the 3-vial formulation?

FDA Response to Question 6a: Study PCR-0003 could not be found in the submission. Although it may be considered as supporting material for the comparison between the (b) (4) and 3-vial formulations, the in vitro drug release profile comparison between them should be conducted and the results provided.

Discussion: Along with pre-clinical data, clinical data may be used to demonstrate comparability of 3-vial and (b) (4) formulations.

Question 6b: Does the Agency agree that the metabolite recently reported does not have to be further characterized for the purposes of the review of the planned NDA in the indication sought?

FDA Response to Question 6b: Additional non-clinical studies are not needed.

Question 13: NDA 21-600 was submitted under the FD&C provisions of 505(b)(2) since the legacy sponsor, Inex (now Tekmira Pharmaceuticals) referenced data which they did not own regarding nonclinical assessment of vincristine sulfate as well as portions of the Oncovin package insert label. Hana plans to reference the same nonclinical data that was utilized by the legacy sponsor as well as portions of the Oncovin package insert label and certify appropriately regarding current patient coverage of the data referenced in accordance with the Agency’s 505(b)(2) guidance. Does the Agency agree that this approach to a 505(b)(2) application and required certifications are appropriate for the planned NDA?

FDA Response to Question 13: If you intend to submit a 505(b)(2) application that relies for approval on FDA’s finding of safety and/or effectiveness for one or more listed drugs (e.g. Oncovin), you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a “bridge” (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval (e.g., the referenced data regarding nonclinical assessment as you note in your question), you also must establish that reliance on the studies described in the literature is scientifically appropriate.

Question 14: The provisions of Fast Track designation are understood to include the possibility of NDA ‘rolling review’ provided that the Agency accepts both the proposed reviewable unit and the proposed schedule of submission of the planned NDA. Hana believes that Module 4 will be available prior to Modules 3 and 5 and proposes that rolling review be considered for the planned Marqibo NDA (see Section 1, Integrated Timeline). Does the Agency agree that provided that the proposed reviewable units and planned NDA submission schedule are agreeable to FDA that a rolling review may be considered?

FDA Response to Question 14: Please see response to Question 1.

3.0 ADDITIONAL FDA COMMENTS

1. Since vincristine is primarily metabolized by CYP3A, we recommend that you conduct clinical drug-drug interaction trials using a strong CYP3A inhibitor (e.g. ketoconazole) and a strong CYP3A inducer (e.g. rifampin) to determine the influence of strong CYP3A4 inhibitors and inducers on the exposure of vincristine.

2. In vitro release (IVR) method development report should be provided in which the conditions for IVR and the acceptance criteria are justified. Notably, the acceptance criteria based on [REDACTED] ^{(b) (4)} would result in very permissive acceptance windows and therefore, is not acceptable.

4.0 ATTACHMENTS AND HANDOUTS

HBS407 Treatment Scenarios Slide presented by Hana Biosciences

Amy Baird
Regulatory Project Manager
Minutes Recorder

Patricia Cortazar, M.D.
Clinical Team Leader
Meeting Chair

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

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

/s/

AMY C BAIRD
11/03/2010

PATRICIA CORTAZAR
11/03/2010