

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202497Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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

PMR Description: 1910-1
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) 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

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Efficacy trial per subpart H.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Efficacy trial per subpart H.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Randomized controlled trial (RCT) of marqibo versus generic vincristine in the second relapse ALL setting in adults, with OS as the primary outcome.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
Efficacy RCT
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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.
1910-2

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

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

To date, the drug has been prepared in pharmacies with experience in handling investigational cancer drug products and with dedicated pharmacy staff, duplicate cabinets for drug preparation, and trained personnel for whom the multiple preparation steps did not present insurmountable difficulties thus far. The complexity of preparation is evident in the multiple revisions necessary to arrive at a detailed and comprehensible set of preparation steps, required materials, and timing of successive steps. Additionally, we received varying advice from the Applicant about who should prepare this product and under what facility conditions (training, equipment, cabinet, and shelving etc.). The circumstances under which this product can be prepared routinely in practice are uncertain.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the survey is to obtain data of post-marketing experience from facilities that use this product. This data will be used to monitor for any difficulties and medication errors due to the unusual preparation of this product. Knowledge gained from this survey may also provide insight to improve the labeling. However, at an internal team meeting, Dr Jenkins advised the data needed would best be obtained via a PMC.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study:** all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial:** any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

See above for the information needed.

Required

- Observational pharmacoepidemiologic study
 Registry studies
 Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 Pharmacokinetic studies or clinical trials
 Drug interaction or bioavailability studies or clinical trials
 Dosing trials
 Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 Immunogenicity as a marker of safety
 Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 Dose-response study or clinical trial performed for effectiveness
 Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs? Yes
- Are the objectives clear from the description of the PMR/PMC? Yes
- Has the applicant adequately justified the choice of schedule milestone dates? Yes
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process? Yes

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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.
1910-3

PMR/PMC Schedule Milestones:	Preliminary Protocol Submission	<u>12/2012</u>
	Final Protocol Submission	<u>6/2013</u>
	Study Completion	<u>12/2016</u>
	Study Report Submission to FDA	<u>6/2017</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

To date, the drug has been prepared in pharmacies with experience in handling investigational cancer drug products and with dedicated pharmacy staff, duplicate cabinets for drug preparation, and trained personnel for whom the multiple preparation steps did not present insurmountable difficulties thus far. The complexity of preparation is evident in the multiple revisions necessary to arrive at a detailed and comprehensible set of preparation steps, required materials, and timing of successive steps. During the review process, product redesign was not feasible despite previous requests.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The drug has been prepared in pharmacies with experience in handling investigational cancer drug products and with dedicated pharmacy staff, duplicate cabinets for drug preparation, and trained personnel for whom the multiple preparation steps did not present insurmountable difficulties thus far. The complexity of preparation is evident in the multiple revisions necessary to arrive at a detailed and comprehensible set of preparation steps, required materials, and timing of successive steps. The goal of this PMC is to simplify preparation in order to minimize the likelihood of medication errors.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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
08/08/2012

505(b)(2) ASSESSMENT

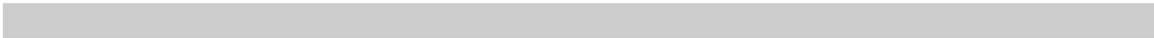
Application Information		
NDA # 202497	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Marqibo Established/Proper Name: vincristine sulfate liposomes injection Dosage Form: Injection Strengths: 2.25mg/m ²		
Applicant: Talon Therapeutics		
Date of Receipt: 7/2/2011		
PDUFA Goal Date: 5/12/2012		Action Goal Date (if different):
Proposed Indication(s): Treatment of Philadelphia Chromosome-negative (Ph-) Adult Acute Lymphoblastic Leukemia (ALL) patients in second or greater relapse or whose disease has progressed following two or more anti-leukemia therapies		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Published literature	Nonclinical publications that summarize vincristine genotoxicity/mutagenicity
Oncovin	Various sections of labeling

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Yes, the scientific rationale is acceptable.

A BA/BE study is not required because the PK profile is expected to be different from liposomal vincristine and non-liposomal formulation. The 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. In addition, animal studies indicate that the toxicity profiles of vincristine and Marqibo are comparable.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If “NO,” proceed to question #5.

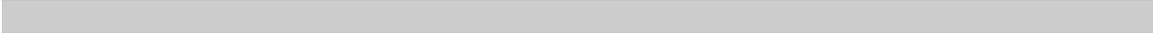
- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If “NO,” proceed to question #5.

If “YES”, list the listed drug(s) identified by name and answer question #4(c).

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?
YES NO



RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Oncovin	NDA 014103	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing: NDA 014103 Oncovin

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a new indication. Marqibo provides for the treatment Philadelphia Chromosome-negative (Ph-) Adult Acute Lymphoblastic Leukemia (ALL) patients in second or greater relapse or whose disease has progressed following two or more anti-leukemia therapies. Oncovin provided for the treatment of patients with aggressive non-Hodgkin's lymphoma.

Application also provides for a new formulation (3 vial kit and change from IR to SR).

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "NO" to (a) proceed to question #11.

If "YES" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?
YES NO

If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO
If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?
YES NO

There are generic vincristine sulfate injection products listed in the Orange Book.

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in

the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s): 4,619,935

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR

314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

- (a) Patent number(s):
- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]? YES NO

If "NO", please contact the applicant and request the signed certification.

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt. YES NO

If "NO", please contact the applicant and request the documentation.

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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/s/

AMY C BAIRD
08/06/2012

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Consumer Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: July 31, 2012

To: Amy Baird – Regulatory Project Manager
Division of Hematology Products

From: Richard Lyght, Pharm.D. – Regulatory Review Officer
Division of Consumer Drug Promotion (DCDP)

Subject: DCDP comments on draft Marqibo (vinCRISStine sulfate
LIPOSOME) injection, Patient Information
NDA 202497

This consult is in response to DHP's March 2, 2012, request for DCDP review of the draft Marqibo labeling.

Comments on the proposed prescribing information (PI) and carton and container labeling will be provided under separate cover.

We have no comments at this time for the proposed Patient Information section provided by DMPP via e-mail on July 31, 2012.

DCDP appreciates the opportunity to provide comments. If you have any questions, please contact Richard Lyght at 301-796-2874 or at richard.lyght@fda.hhs.gov.

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/s/

RICHARD A LYGHT
07/31/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: July 31, 2012

To: Ann Farrell, MD
Director
Division of Hematology Products (DHP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon R. Mills, BSN, RN, CCRP
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: DMPP Review of Patient Labeling: Patient Package Insert
(PPI)

Drug Name (established name): Marqibo (vinCRISTine sulfate LIPOSOME injection)

Dosage Form and Route: for intravenous infusion

Application Type/Number: NDA 202-497

Applicant: Talon Therapeutics, Inc.

1 INTRODUCTION

On July 12, 2011 Talon Therapeutics, Inc submitted for the Agency's review New Drug Application (NDA) 202-497 for Marqibo (vinCRISTine sulfate LIPOSOME injection). The proposed indication for Marqibo (vinCRISTine sulfate LIPOSOME injection) is for the treatment of adult patients with Philadelphia chromosome-negative (Ph-) acute lymphoblastic leukemia (ALL) in second or greater relapse or whose disease has progressed following two or more anti-leukemia therapies. On September 23, 2011, the Division of Hematology Products (DHP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for Marqibo (vinCRISTine sulfate LIPOSOME injection).

This review is written in response to a request by DHP for DMPP to review the Applicant's proposed Patient Package Insert (PPI) for Marqibo (vinCRISTine sulfate LIPOSOME injection).

2 MATERIAL REVIEWED

- Draft Marqibo (vinCRISTine sulfate LIPOSOME injection) Patient Package Insert (PPI) received from the Review Division on July 17, 2012.
- Draft Marqibo (vinCRISTine sulfate LIPOSOME injection) Prescribing Information (PI) received on July 12, 2011, revised by the Review Division throughout the review cycle, and received by DMPP on July 17, 2012.

3 REVIEW METHODS

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. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the PPI is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

10 Page(s) of Draft Labeling have 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/

SHARON R MILLS
07/31/2012

BARBARA A FULLER
07/31/2012

LASHAWN M GRIFFITHS
07/31/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Review

Date: July 26, 2012

Reviewer: Jibril Abdus-Samad, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Todd Bridges, RPh
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Marqibo (Vincristine Sulfate Liposome Injection)
0.16 mg/mL following reconstitution

Application Type/Number: NDA 202497

Applicant: Talon Therapeutics

OSE RCM #: 2011-3508

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

Executive Summary	1
1 Introduction.....	2
1.1 Product Information	2
2 Previous Marqibo Medication Error Reviews	3
2.1 NDA 021600.....	4
2.2 IND 059056	6
3 NDA 202497 - Review Timeline.....	9
4 Discussion.....	12
5 Conclusions.....	15
References.....	16
Appendices.....	17

EXECUTIVE SUMMARY

DMEPA has been concerned with the overall product design and proposed product preparation procedures for Marqibo since our first consultation in 2003. Due to the following medication error concerns, we requested a product redesign prior to approval.

The proposed product requires encapsulation of vincristine into liposomes and the concentration of free vincristine is critically dependent upon the accurate preparation of this liposomal formulation. Specifically, deviating from the specified procedures regarding the time and temperature ranges required during preparation 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 may cause a serious risk to patients because the liposomal formulation is dosed considerably higher than the non-liposomal formulation of vincristine.

Moreover, the equipment required to prepare Marqibo including a hot water bath, calibrated thermometer, and timer are not typically available in inpatient pharmacies, outpatient chemotherapy centers, or general oncology practices. DMEPA is 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.

Additionally, environmental influences may further interfere with the correct use of the equipment, including work place interruptions, distractions, and inadequate staffing as well as sterility recommendations required by USP 797 and the Joint Commission for intravenous product preparation.

The Human Factors (HF) study conducted by the applicant did not assure us that the pharmacies studied could be considered representative of the nation nor could they confirm that the general preparation of Marqibo could be routinely performed with sterility and safety in diverse settings. We also learned the following from the clinical trial sites:

- Pharmacy technicians and pharmacists prepare product
- Preparation is somewhat burdensome, required dedicated pharmacy technician and pharmacist time
- No personnel performed other tasks during preparation of Marqibo
- Preparation required advanced planning

Because re-formulation of this product was not feasible despite the numerous requests prior to approval, we required labeling revisions so the preparation instructions are clear, concise, and work within the medication use system. The preparation instructions have been revised to:

- Provide recommendations for the placement, use, and cleaning of the water bath
- Provide recommendations regarding movement of the vial in and out of the sterile field and how to maintain sterility for the final drug preparation in IV bag
- Include information from clinical trials that Marqibo preparation required a dedicated person to monitor temperature and time accurately and to prevent distractions
- Provide information that encapsulation of vincristine into the liposome is time and temperature dependent.
- Provide directions for when deviations outside the temperature and time parameters occur during preparation.
- Provide advice regarding how to handle equipment failure.

Moreover, we were able to have the Applicant commit to the following:

- Supply the water bath, thermometer, and timer on first purchase and replace them every 2 years
- 1-800-xxx-xxxx for problems or questions with Marqibo
- Postmarketing commitment to explore other design options to simplify preparation of Marqibo, including the possibility of developing a formulation of liposomal encapsulation such that the step of heating of the drug in the pharmacy is eliminated and to survey pharmacies in order to obtain post-marketing experience from facilities that use this product. This data will be used to monitor for any difficulties and medication errors due to the unusual preparation of this product. Knowledge gained from this survey may also provide insight to improve the instructions for use in the labeling.

1 INTRODUCTION

This review summarizes the DMEPA medication error evaluations conducted for Marqibo (vincristine sulfate liposome injection) since first consulted in 2003.

1.1 PRODUCT INFORMATION

Marqibo is a kit for preparation of Vincristine Sulfate Liposome Injection. The kit contains the following:

- Vincristine Sulfate Injection, USP, 5 mg/5 mL (1 mg/mL)
- Sphingomyelin/Cholesterol Liposome Injection, 103 mg/mL
- Sodium Phosphate Injection, 355 mg/25 mL (14.2 mg/mL)
- The three component vials are packaged in a single Marqibo Kit that includes the Marqibo Package Insert Label, Flotation Ring, Overlabel for Sodium Phosphate Injection vial containing constituted Marqibo (vincristine sulfate liposome injection, 0.16 mg/mL), and Infusion Bag Label as the drug product.
- Marqibo (Vincristine sulfate liposome injection, 0.16 mg/mL) is compounded in accordance with the Package Insert Label at the dispensing pharmacy.

- Indication of Use: treatment of adult patients with Philadelphia Chromosome-negative acute lymphoblastic leukemia in second or greater relapse or whose disease has progressed following two or more treatment lines of anti-leukemia therapy.
- Dose and Frequency: 2.25 mg/m² intravenously over 60 minutes every 7 days. Dose reductions from non-hematologic toxicity are 2 mg/m², 1.825 mg/m², and 1.5 mg/m² intravenously over 60 minutes every 7 days for Grade 2 or better non-hematologic toxicity
- How Supplied: The Marqibo Kit for preparation of Vincristine Sulfate Liposome Injection is composed of:
 - Vincristine Sulfate Injection, USP, 5 mg/5 mL (1 mg/mL)
 - Sphingomyelin/Cholesterol Liposome Injection, 103 mg/mL
 - Sodium Phosphate Injection, 355 mg/25 mL (14.2 mg/mL)
 - The three component vials are packaged in a single Marqibo Kit that includes the Marqibo Package Insert Label, Flotation Ring, Overlabel for Sodium Phosphate Injection vial containing constituted Marqibo (vincristine sulfate liposome injection, 0.16 mg/mL), and Infusion Bag Label as the drug product. The Marqibo (Vincristine sulfate liposome injection, 0.16 mg/mL) is compounded in accordance with the Package Insert Label at the dispensing pharmacy.
- Storage: Refrigerate at 2°C to 8°C – Do Not Freeze
- Container and Closure System:
 - Vincristine Sulfate Injection, USP: 5 mL glass vial
 - Sphingomyelin/Cholesterol Liposome Injection: 3 mL glass vial
 - Sodium Phosphate Injection: 30 mL glass vial

Additionally, the insert labeling suggests the following:

- Pharmacy-supplied items
 - Calibrated thermometer (0°C to 100°C)
 - Calibrated electronic timer
 - Vented needle or other suitable device equipped with a 0.2 micron filter
 - 1 mL or 3 mL sterile syringe with needle
 - 5 mL sterile syringe with needle

2 PREVIOUS MARQIBO MEDICATION ERROR REVIEWS

DMEPA provided comment on the product design of Marqibo in several reviews prior to the filing of the current NDA submitted by Talon. The following summarizes these communications.

2.1 NDA 021600

In October of 2003, DMEPA (formerly DMETS) was requested to evaluate the proposed proprietary name Marqibo, which was originally submitted under NDA 021600 from Inex Pharmaceuticals. At the time of this review, there were no labels and labeling available for evaluation but based on the description of the product we were concerned with the proposed product design. The following three concerns were first outlined in January 13, 2004 (OSE Review 03-0210):

- **Packaging Configuration**
DMETS has concerns that the proposed packaging configuration increases the potential for errors due to the omission of one or more drug components prior to administration. The proposed kit contains one vial of vincristine sulfate injection, USP (1 mg/mL, 5 mL), one vial of sphingomyelin/cholesterol liposomes injection (103 mg/mL, 1 mL), and one vial of sodium phosphate injection (14.2 mg/mL, 25 mL). DMETS questions the potential for error and harm if one or more of the components are inadvertently omitted from the preparation of the final drug product. In addition, the procedure for adding the various components of the drug product is unclear. Therefore, we question the potential for error and harm if the ingredients are not mixed in a particular order. The sponsor should address patient safety issues should this occur.
- **Potential Vincristine Formulation Confusion**
DMETS is also concerned that name “Marqibo” does not provide any indication that the product contains vincristine sulfate as do other vincristine alkaloid products (*Vincosar and Oncovin*). Also, although Marqibo contains vincristine, the recommended dose differs from the currently marketed vincristine. DMETS has concerns that health professionals may administer Marqibo in doses identical to that of vincristine injection because of the unfamiliarity of this liposomal formulation. A similar situation exists with conventional Amphotericin B and Amphotericin B liposomal formulation, which also differ in dose. Medication errors have been reported in which patients have received either an overdose or under dose of medication due to confusion between the products and their respective dosing. These errors have resulted in patients experiencing sepsis, cardiac arrest, and even death. Therefore, in order to prevent these types of errors from occurring with Marqibo and vincristine injection, the sponsor should outline in detail the steps that will be taken to educate health care professionals concerning the difference in formulation and dosing.
- **Established Name**
The proposed established name, vincristine sulfate liposome injection, indicates that the active ingredient contains the liposomes as opposed to the active ingredient and liposomes existing in separate containers as proposed. Therefore, we recommend that the Division consult Dan Boring, Chair of the CDER Labeling and Nomenclature Committee with regard to the proper designation of the established name.

In November 2004, DMEPA was re-consulted to evaluate the proprietary name and we noted that the concerns stated in the previous review were not addressed. Therefore, we restated the following concerns with regard to the packaging configuration and product formulation in OSE 03-0210-1:

- DMETS has concerns that the proposed packaging configuration increases the potential for errors due to the omission of one or more drug components prior to administration. The proposed kit contains one vial of vincristine sulfate injection, USP (1 mg/mL, 5 mL), one vial of sphingoliposomes injection (103 mg/mL, 1 mL), and one vial of sodium phosphate injection (14.2 mg/mL, 25 mL). DMETS questions the potential for error and harm if one or more of the components are inadvertently omitted from the preparation of the final drug product. Additionally, this product has complex and numerous steps to follow which will contribute to user error.
 - DMETS is concerned regarding the number of steps involved with preparing this drug product, as the more steps involved with preparation, the higher the chance of confusion and error. We question why the liposome will not be manufactured with the active ingredient, eliminating the need for the constitution of the drug product by the pharmacy? This concern is further heightened since practitioners may believe that an unconstituted vial has been constituted and is ready for administration. We also have had many errors with products that are packaged with diluent alone. This product will have an additional step. Increasing the number of steps may increase the likelihood for this type of error.
 - DMETS is concerned that if the "required materials not supplied in the kit" (i.e., water bath, thermometer, stopwatch or timer, sterile syringes, sterile venting filter needles) are not available, 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.
- Although Marqibo contains vincristine, the recommended dose differs from the currently marketed vincristine. DMETS has concerns that health professionals may administer Marqibo in doses identical to that of vincristine injection because of the unfamiliarity of this liposomal formulation. A similar situation exists with conventional Amphotericin B and Amphotericin B liposomal formulation, which also differ in dose. Medication errors have been reported in which patients have received either an overdose or underdose of medication due to confusion between the products and their respective dosing. These errors have resulted in patients experiencing sepsis, cardiac arrest, and even death. Therefore, in order to prevent these types of errors from occurring with Marqibo and vincristine injection, the sponsor should outline in detail the steps that will be taken to educate health care professionals concerning the difference in formulation and dosing.

- Established Name - The proposed established name, vincristine sulfate liposome injection, indicates that the active ingredient contains the liposomes as opposed to the active ingredient and liposomes existing in separate containers as proposed. Therefore, we recommend that the Division consult Guiragos Poochikian, Acting Chair of the CDER Labeling and Nomenclature Committee with regard to the proper designation of the established name.

In January 14, 2005, NDA 021600 received a Not Approvable Action for Clinical and Chemistry, Manufacturing, and Controls concerns which included comments from DMEPA on a separate fax.

2.2 IND 059056

In January 4, 2010, the Marqibo name was re-evaluated under IND 059056 by Hana Biosciences Inc. At that time, DMEPA reiterated the following concerns with the design of Marqibo with respect to medication errors (see OSE review 2008-1983):

- Although we did not identify concerns regarding confusion with the proposed proprietary name from a sound and look-alike potential, the FMEA demonstrated that the different product characteristics and similarity of the established name (Vincristine Sulfate Liposomes Injection) of Marqibo when compared to the currently marketed Vincristine product make the products vulnerable to confusion that can lead to medication errors. DMEPA is concerned that prescribers will write for 'Vincristine injection' and that medication errors will arise due to confusion as to which product to dispense (i.e. currently marketed Vincristine products or the proposed Liposomes for injection). A similar situation exists with conventional Amphotericin B and Amphotericin B liposomal formulation, which also differ in dose. Medication errors have been reported in which patients have received either an overdose or underdose of medication due to confusion between the products and their respective dosing. These errors have resulted in patients experiencing sepsis, cardiac arrest, and even death. Therefore, in order to prevent these types of errors from occurring with Marqibo and vincristine injection, the sponsor should outline in detail the steps that will be taken to minimize the risk of confusion between these products at the time of submission of the NDA. DMEPA is willing to include this concern in our communication to the Sponsor regarding the proprietary name Marqibo.
- DMEPA is also concerned with the complexity of preparation of the product since the content of three separate vials will need to be combined prior to administration. Since the sponsor has not submitted detail steps on the preparation process DMEPA is unable to evaluate the process at this time, however DMEPA will evaluate the preparation process and the labels and labeling when they are available in a separate review.

In April 2010, DMEPA attended a pre-NDA meeting and provided the following comments to the Division per their request in August 1010 (OSE review 2010-806):

We recommended the following issues be addressed in their NDA submission.

- 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)

[REDACTED] 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.

- 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.

- 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 requirements.

- 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 with 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.

- 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).

In April 2010, DOP1 (formerly DDOP) forwarded a 02/02/2010 submission from Applicant in response to 1/14/2005 comments from DMEPA. Of note the Applicant states, “We agree with DMETS staff that the single vial approach could be an improvement with regard to potential issues notes in DMETS comments.”

3 NDA 202497 - REVIEW TIMELINE

Aug 19, 2010 DMEPA emailed pre-NDA comments regarding product design. We requested the concerns be sent to the Applicant. This comments highlighted potential medication error issues during all phases of the medication use process (procurement, prescribing, preparation, dispensing, and administration).

Aug 26, 2010 DMEPA completed a Medication Error Review which contained the comments detailed above in above in 8/19/2010 and signed in DARRTS. Of note, these comments were not sent to the Applicant until 12/14/2011.

Jul 12, 2011 NDA 202497 submitted.

Sep 23, 2011 DMEPA received proprietary name and labeling assignment.

Oct 17, 2011 DMEPA emailed DHP regarding safety concerns.

Nov 16, 2011 DMEPA asks DHP if Applicant received our previous comments because the submission did not address our previously communicated concerns.

Dec 01, 2011 DMEPA requests DHP send Applicants our comments.

Dec 07, 2011 DMEPA requests data of Marqibo if prepared outside of recommended conditions.

Dec 14, 2011 DHP sends DMEPA’s previous comments to the Applicant (Appendix A).

Dec 21, 2011 In a meeting between DMEPA reviewer and DHP Medical Officer (MO), MO not convinced DMEPA concerns are a major issue.

Jan 11, 2012 DHP *denies* DMEPA’s request to meet with DHP Director, Cross Discipline Team Leader, and MO to discuss our safety concerns.

Jan 25, 2012 DMEPA mentioned our concerns during Mid-Cycle meeting. Based on data from clinical studies, it was unlikely product would be approved.

Jan 25, 2012 Applicant submitted a Human Factors study conducted in 2003.

Mar 16, 2012 DMEPA requests sample of Marqibo Kit.

- Mar 21, 2012 ODAC vote 7 yes, 4 no, 2 undecided. Only clinical trial data discussed, however no discussion of Marqibo preparation.
- Mar 22, 2012 DMEPA presents major issues to team during labeling meeting. Dr. Pazdur brought into meeting. OSE PM notifies DRISK of issues.
- Mar 26, 2012 Dr. Pazdur requests respective disciplines consult with Senior Management. During this meeting, DHP PM clarified that the clinical team previously decided to hold all meetings until after the ODAC, therefore all the meetings were pushed back.
- Mar 28, 2012 DHP sent Information Request (IR) to Applicant containing DMEPA deficiencies that concerns with equipment, procedure for preparation, container label, carton and insert labeling, and requested the Applicant conduct further HF studies and submit a revised protocol for review prior to initiation (Appendix B).
- Apr 3, 2012 DMEPA sent further IR for a HF study to address deficiencies from first HF study. This IR was subsequent to internal team meetings in which DMEPA was requested to provide specific details on what the HF study protocol should include (Appendix C).
- Apr 11, 2012 DMEPA and ONDQA sent combined Container Label and Carton Labeling Deficiencies (Appendix D).
- Apr 17, 2012 DMEPA sent a response to Applicant's revised HF Study Protocol (Appendix E).
- Apr 24, 2012 Face-to-face meeting with Applicant to discuss HF study.
- Apr 25, 2012 DMEPA sends IR for description of facilities, workflow, and issues at the clinical sites that prepared Marqibo in your clinical trials (Appendix F).
- Apr 30, 2012 The Division of Risk Management (DRISK) and DMEPA sent questions to federal partner, National Institutes of Health (NIH).
- May 3, 2012 DMEPA and DRISK received responses to a questionnaire about experience with Marqibo preparation from NIH (Appendix G).
- May 3, 2012 DMEPA and DRISK held a teleconference with NIH to discuss their experience with Marqibo preparation.
- May 3, 2012 In an internal meeting with DHP, DRISK, and DMEPA, DHP recommended improving the preparation instructions instead of requiring an additional HF study prior to approval. Therefore, we subsequently revised the Marqibo labeling considering the responses and recommendations from NIH and the Office of Compliance to improve the labeling of Marqibo along with recommending a Post Marketing Commitment (PMC) for the Applicant to provide a survey of post-marketing experience of Marqibo preparation.
- May 23, 2012 DHP sent PMC for survey of post-marketing experience of Marqibo preparation to the Applicant (Appendix H).

- Jun 11, 2012 DMEPA attended labeling meeting with DHP. DHP agreed with DMEPA's recommendations to the insert labeling.
- Jun 13, 2012 DMEPA sent email to DHP agreeing to the team's proposal for a PMC to explore methods to simplify preparation of the Marqibo, including the possibility of developing a formulation of liposomal encapsulation that eliminates heating of the drug during preparation.
- Jun 14, 2012 DMEPA and ONDQA provided recommendations to the updated container labels and carton labeling to DHP to be sent to the Applicant (Appendix I).
- Jul 10, 2012 DMEPA sent email to DHP inquiring about status of carton and container labels and labeling from Applicant
- Jul 17 2012 Applicant submits revised container labels, carton, and insert labeling.
- Container Label for Vincristine Sulfate Injection (Appendix J)
 - Container Label for Sodium Phosphate Injection (Appendix K)
 - Container Label for Sphingomyelin-Cholesterol Liposome Injection (Appendix L)
 - Carton Labeling for Marqibo (Appendix M)
 - Overlabel (Appendix N)
 - Intravenous Bag Label (Appendix O)
- Jul 18, 2012 DMEPA and ONDQA provided additional recommendations to the updated container labels and carton labeling for DHP to send to the Applicant (Appendix P).
- Jul 19, 2012 DMEPA emailed DHP and CMC to state PMC #1 is acceptable but the timelines for PMC #2 should be shorter.
- Jul 19, 2012 Applicant provided PMR and PMC proposals.
- Jul 24, 2012 DMEPA proposes revised timeline for PMC #2 and CMC concurs. DHP will send to Applicant for their response/concurrence.
- Jul 26, 2012 DMEPA Label and Labeling review submitted in DARRTS. The Applicant's response to Container labels and Carton labeling revisions are still pending. Additionally, one labeling meeting is scheduled for July 30, 2012 for completion of the insert labeling.

4 DISCUSSION

The proposed product requires encapsulation of vincristine into liposomes and the concentration of free vincristine is critically dependent upon the accurate preparation of this liposomal formulation. Specifically, deviating from the specified procedures regarding the time and temperature ranges required during preparation 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 may cause a serious risk to patients since the liposomal formulation is dosed considerably higher than the non-liposomal formulation of vincristine. For these reasons, we have been concerned with the overall product design and proposed preparation procedures of this product for the past decade.

The equipment required to prepare Marqibo 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. DMEPA is 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.

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, distractions, and inadequate staffing as well as sterility recommendations required by USP 797 and the Joint Commission for intravenous product preparation.

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.

Moreover, the constitution procedures are composed of numerous steps and 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 incorporate this process into their practice to routinely and safely preparing of the drug. The Applicant stated that only pharmacists would prepare this product and that it would not be used in oncology clinics.

Additionally, the Applicant stated they conducted a Human Factors study; however, this study did not include two key end user groups, pharmacy technicians and oncology nurses. These two groups currently prepare chemotherapy in medical facilities. Additionally, the protocol failed to include the following two tasks that are critical for the safe administration of the product.

- Product selection from the refrigerator shelf
This is critical because of the potential for product selection errors previously encountered with other liposomal and non-liposomal products. Confusion between Marqibo and non-liposomal formulations of vincristine represents a serious risk to patients due to differences in dosing.
- Preparation of doses less than or greater than 5 mg
Doses less than 5 mg will require calculation and for doses greater than 5 mg constitution using 2 kits of your product. These tasks may have added risks or potential errors than constitution of 1 kit or using the total contents of a single vial.

Furthermore, the HF Study Questionnaire lacked qualitative responses. Not verbatim responses were collected with respect to questions concerning product preparation. Additionally, in section 7.1 - Pharmacy Study of Marqibo Constitution by Pharmacists Naive to the Constitution Process, there were no details regarding the accidental spillage that occurred at four sites, errors at two sites, and specifically what task was to be done on Step 11, which was omitted in the preparation process.

Based on the Human Factors study, we were not assured that the pharmacies studied could be considered representative and confirm that the general preparation of Marqibo could be routinely performed with sterility and safety in diverse settings. Because we could not require the Applicant to conduct another Human Factors study prior to approval, we asked the Applicant to survey the sites using Marqibo in the clinical trials for their experience with the product. We learned the following from the clinical trial sites:

- Pharmacy technicians and Pharmacists prepare product
- Preparation is somewhat burdensome, required dedicated pharmacist time
- No personnel performed other tasks during preparation of Marqibo
- Required advanced planning

Because re-formulation of this product is not feasible prior to approval, the preparation instructions must be clear, concise, and work within the medication use system. The instructions must have specificity with respect to:

- Provide recommendations for the placement, use, and cleaning of the water bath
- Provide recommendations regarding movement of the vial in and out of the sterile field and how to maintain sterility for the final drug preparation in IV bag
- Include information from clinical trials that Marqibo preparation required a dedicated person to monitor temperature and time accurately and to prevent distractions
- Provide information that encapsulation of vincristine into the liposome is time and temperature dependent.
- Provide directions for when deviations outside the temperature and time parameters occur during preparation.
- Provide advice regarding how to handle equipment failure.

Ideally, Marqibo should have been redesigned to a product in which Vincristine Sulfate is already encapsulated into the liposome and/or require multiple constitutions of three separate vials and heating. [REDACTED] ^{(b) (4)} we were able to have the applicant commit to the following:

- Supply the water bath, thermometer, and timer on first purchase and replace them every 2 years
- 1-800-xxx-xxxx for problems or questions with Marqibo
- Postmarketing commitment to explore other design options to simplify preparation of Marqibo, including the possibility of developing a formulation of liposomal encapsulation such that the step of heating of the drug in the pharmacy is eliminated and to survey pharmacies in order to obtain post-marketing experience from facilities that use this product. This data will be used to monitor for any difficulties and medication errors due to the unusual preparation of this product. Knowledge gained from this survey may also provide insight to improve the instructions for use in the labeling.

At the time this review was completed, we have yet to receive the final version of the labels and labeling.

5 CONCLUSIONS

DMEPA aligns with the proposal to have the Applicant conduct a survey of post-marketing experience of Marqibo preparation (Appendix H) and to explore methods to simplify preparation of the Marqibo, including the possibility of developing a formulation of liposomal encapsulation that eliminates heating of the drug during preparation as part of postmarketing commitment. We await the final revisions to the labels and labeling.

REFERENCES

1. Abate, Richard. OSE Review 2010-806. Pre-IND Medication Error Review for Marqibo. August 26, 2010
2. Oleszczuk, Zachary. OSE Review 2008-1983. Proprietary Name Review for Marqibo. January 4, 2010
3. Roselle, Nora. OSE Review 03-0210-1. Proprietary Name Review for Marqibo. November 30, 2004
4. Harper-Valazquez, Tia M. OSE Review 03-0210. Proprietary Name Review for Marqibo. January 13, 2004

APPENDICES

Appendix A: IR detailing DMEPA's previous comments on December 14, 2012

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 your NDA submission.

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 “(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 (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 with 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).

Appendix B: March 28, 2012 IR

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.



- 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 m², 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. (b) (4)

Please clarify this discrepancy.
 - B. Revise the statement (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:
 (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.

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Appendix D: DMEPA and ONDQA sent combined Container Label and Carton Labeling Deficiencies

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
(vinCRIS^tine 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

(vinCRIS^tine sulfate LIPOSOME injection)

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Appendix F: DMEPA IR for description of facilities, workflow, and issues at the clinical sites that prepared Marqibo in your clinical trials

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?

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Appendix H: Post-Marketing Commitment sent May 23, 2012

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA #/Product Name: NDA 202497 Marqibo

PMC Description: 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 6 month intervals on the experience of health care practitioners (HCPs) regarding safety or technical problems with preparation of Marqibo in practice settings. (b) (4)

[Redacted]

[Redacted] (b) (4)

PMC Schedule Milestones:	Preliminary study Protocol Submission	<u>MM/YYYY</u>
	Final Protocol Submission:	<u>MM/YYYY</u>
	Interim study reports	<u>Every 6 months</u>
	Study Completion:	<u>08/2017</u>
	Final Report Submission:	<u>MM/YYYY</u>
	Other: _____	<u>MM/YYYY</u>

During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

To date, the drug has been prepared in pharmacies with experience in handling investigational cancer drug products and with dedicated pharmacy staff, duplicate cabinets for drug preparation, and trained personnel for whom the multiple preparation steps did not present insurmountable difficulties thus far. The complexity of preparation is evident in the multiple revisions necessary to arrive at a detailed and comprehensible set of preparation steps, required materials, and timing of successive steps. Additionally, we received varying advice from the Applicant about who should prepare this product and under what facility conditions (training, equipment, cabinet, and shelving etc.). The circumstances under which this product can be prepared routinely in practice are uncertain.

Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the survey is to obtain data of post-marketing experience from facilities that use this product. This data will be used to monitor for any difficulties and medication errors due to the unusual preparation of this product. Knowledge gained from this survey may also provide insight to improve the labeling. However, at an internal team meeting, Dr Jenkins advised the data needed would best be obtained via a PMC.

If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

See above for the information needed.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial
(provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

Other

Conditions of use monitoring

Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Appendix I: Container Labels and Carton Labeling recommendations sent June 12, 2012

A. General Comment

Add a bar code to each of the vial container labels and carton labeling to be in compliance with 21 CFR 201.25.

B. Carton Labeling

1. De-bold the strength statements for all the vials that appear on the principal display panel.

2. Revise the established name, [REDACTED] (b) (4)

3. Revise the statement, FOR INTRAVENOUS USE ONLY, FATAL IF GIVEN BY OTHER ROUTES, to Title Case to appear as follows:

For Intravenous Use Only
Fatal If Given By Other Routes

4. Include only one Infusion Bag Label. The intravenous bag containing diluted Marqibo must have space for the medical facility or pharmacy label.

C. Sodium Phosphate Injection Container Label

1. Revise the strength statement, 355 mg/25 mL (14.2 mg/mL), to orange-color font with a white background similar to the presentation of the established name to improve readability. Currently, the strength is difficult to read.

2. Relocate the strength statement to appear after the established name. Thus, the established name and strength should appear as follows:

Sodium Phosphate Injection
355 mg/25 mL (14.2 mg/mL)
for use only in the preparation of Marqibo

3. Delete the statement, [REDACTED] (b) (4) The volume of 25 mL is already expressed in the strength statement

4. De-bold the statement Single Use Vial - Discard Unused Portion.

D. Sphingomyelin-Cholesterol Liposome Injection Container Label

1. Remove parenthesis from the strength statement, (103 mg/mL).
2. Revise the strength statement, 103 mg/mL, to blue-color font with a white background similar to the presentation of the established name to improve readability. Currently, the strength is difficult to read.
3. Relocate strength to appear after the established name. Thus, the established name and strength should appear as follows:

Sphingomyelin-Cholesterol Liposome Injection
103 mg/mL
for use only in the preparation of Marqibo

4. Delete the storage information. The storage information is not required on small labels. Additionally, the storage information is already on the outer carton label of Marqibo.
5. Delete the statement, (b) (4). The volume is already expressed in the strength statement
6. De-bold the statement Single Use Vial - Discard Unused Portion.

E. Vincristine Sulfate Injection Container Label

1. Revise the established name, VinCRISTine Sulfate Injection, USP, (b) (4)
2. Revise strength statement, 5 mg/5 mL (1 mg/1 mL) to read 5 mg/5 mL (1 mg/mL). Additionally, revise the strength statement, 5 mg/5 mL (1 mg/mL), to green/brown-color font with a white background similar to the presentation of the established name to improve readability. Currently, the strength is difficult to read.
3. Relocate the strength statement to appear after the established name. Thus, the established name and strength should appear as follows:

VinCRISTine Sulfate Injection, USP
5 mg/5 mL (1 mg/mL)
for use in the preparation of Marqibo

4. Delete the storage information. The storage information is not required on small labels. Additionally, the storage information is already on the outer carton label of Marqibo.
5. Delete the statement, [REDACTED] (b) (4) The volume is already expressed in the strength statement
6. De-bold the statement Single Use Vial - Discard Unused Portion.

F. Marqibo Overlabel

1. Improve readability of the strength statement, 5 mg/31 mL (0.16 mg/mL), by revising the strength statement, to green/brown-color font with a white background similar to the presentation of the established name or increase the font size. Currently, the strength is difficult to read.
2. Revise the statement, FOR INTRAVENOUS USE ONLY, FATAL IF GIVEN BY OTHER ROUTES, to Title Case to appear as follows:

For Intravenous Use Only
Fatal If Given By Other Routes

3. Delete the statement, [REDACTED] (b) (4) The volume is already expressed in the strength statement

G. Marqibo Intravenous bag label

1. Revise the statement, FOR INTRAVENOUS USE ONLY, FATAL IF GIVEN BY OTHER ROUTES, to Title Case to appear as follows:

For Intravenous Use Only
Fatal If Given By Other Routes

2. Revise the statements, [REDACTED] (b) (4)
[REDACTED] to read as follows:

Must complete administration by the expiration date and time

Appendix J: Container Label for Vincristine Sulfate Injection



Appendix K: Container Label for Label for Sodium Phosphate Injection



Appendix L: Container Label for Sphingomyelin-Cholesterol Liposome Injection



Appendix M: Carton Labeling for Marqibo

(b) (4)



Appendix N: Overlabel

(b) (4)



Appendix O: Intravenous Bag Label



Appendix P: DMEPA and ONDQA recommendations to the updated container labels and carton labeling

A. Carton Labeling

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

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

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

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/s/

JIBRIL ABDUS-SAMAD
07/26/2012

TODD D BRIDGES
07/26/2012

CAROL A HOLQUIST
07/26/2012

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: June 15, 2012

To: Amy Baird, Regulatory Project Manager
Division of Hematology Products (DHP)

From: Nisha Patel, Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)

Subject: Comments on draft labeling (Package Insert) for Marqibo[®]
(vinCRISTine sulfate LIPOSOME injection) for intravenous infusion
NDA 202497

In response to your consult dated September 26, 2011, we have reviewed the draft Package Insert (PI) for Marqibo and offer the following comments. DPDP has made these comments using the version dated June 12, 2012.

Section	Statement from draft	Comment
Highlights, Indications and Usage		(b) (4)
12.3 Pharmacokinetics		(b) (4)
14. Clinical Studies		

Section	Statement from draft	Comment
	(b) (4)	

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/s/

NISHA PATEL
06/15/2012

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: March 21, 2012

TO: Amy Baird, Regulatory Project Manager
Ashkan Emadi, M.D., Ph.D. Medical Officer
Qin Ryan, M.D., Ph.D. Team Leader
Division of Hematology Products (DHP)

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Acting Division Director
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

FROM: Anthony Orenca, M.D., F.A.C.P.
Medical Officer, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 202497

APPLICANT: Talon Therapeutics Inc.

DRUG: vincristine sulfate liposomes injection (Marqibo®)

NME: No

THERAPEUTIC CLASSIFICATION/REVIEW: Standard Review

INDICATION: treatment of adult patients with Philadelphia chromosome negative acute lymphoblastic leukemia (ALL) in relapse disease following anti-leukemic therapy

CONSULTATION REQUEST DATE: September 28, 2011 (signed)

DIVISION ACTION GOAL DATE: March 23, 2012

PDUFA DATE: May 12, 2012

I. BACKGROUND:

Induction, complete remission, and overall survival are poor in adult acute lymphoblastic leukemia (ALL) patients, particularly in advanced, relapsed or refractory cases. Other agents and formulations, such as the intravenous liposomal formulation of vincristine, have been sought to achieve a potentially longer duration of exposure of tumor cells to therapeutic drug concentrations and presumed enhancement of efficacy. Vincristine encapsulated in a liposome, comprised of sphingomyelin and cholesterol, is slowly released in the tumor interstitium.

Two adequate studies were submitted in support of this NDA submission. Two high enrollment centers for study Protocol HSB-407 and a single high enrollment center for study Protocol VSLI-06 were the subject of clinical audits.

Protocol HSB-407

Study HSB-407 was a Phase 2, international, multicenter, open-label, single-arm trial. The study objective was to evaluate the efficacy of the study treatment as determined by the rate of complete response and complete response with incomplete blood count recovery (CRi) in adult subjects with Philadelphia chromosome-negative (Ph-) ALL in second relapses or adult subjects with (Ph-) ALL who failed two treatment lines of anti-leukemia chemotherapy. Subjects achieved a complete response if they had a leukemia-free interval of 90 days or greater. The primary efficacy endpoint was the proportion of subjects who achieved complete remission and complete remission with incomplete blood count recovery. Complete remission (CR) was defined as a normal bone marrow differential (i.e., 5% or less blasts) or a normalization of the peripheral blood with an absence of leukemia blast cells. The platelet count remained at or above 100×10^9 per L and an absolute neutrophil count remained at or above 1×10^9 per L. Complete remission with incomplete blood count recovery was defined as for complete remission, but the platelet count remained below 100×10^9 per L or an absolute neutrophil count remained below 1×10^9 per L.

Protocol VSLI-06

VSLI-06 was a Phase 1-2, multicenter, open-label, dose escalation study of vincristine sulfate liposomes injection (VSLI) with pulse dexamethasone in patients with ALL. The objective of the study was to determine the maximum tolerated dose of VSLI administered with pulse dexamethasone in subjects with relapsed or refractory ALL, including lymphoblastic lymphoma and Burkitt's subtypes, and to assess the efficacy of VSLI with dexamethasone in subjects with relapsed or refractory ALL. Subjects were required to have relapsed or refractory ALL (including lymphoblastic lymphoma or Burkitt's like-subtypes) and to have measurable disease. The primary efficacy endpoint was the proportion of subjects who achieved complete response, partial response, and the combined response of complete and partial response. Complete response (CR) was the normalization of the peripheral blood or bone marrow with 5% or less blasts in a normocellular or hypercellular marrow. The platelet count remained at or above 100×10^9 per L and an absolute neutrophil count remained at or above 1×10^9 per L. Partial response was defined as per complete remission, but the bone marrow blasts had percentage counts of between 6 and 25%.

II. RESULTS (by protocol/site):

Name of CI	City, State	Protocol/Study Site#/ # of subjects	Insp. Date	Final Classification
Gary John Schiller, M.D.	Los Angeles, CA	Protocol HSB-407 Site #026/ Subjects: 9	11/29/2011- 2/5/2012	VAI
Stuart Goldberg, MD	Hackensack, NJ	Protocol HSB-407 Site #193/ Subjects: 5	10/31-11/14, 2011	NAI
Susan O'Brien, MD	Houston, TX	Protocol VSLI-06 Site #001 Subjects: 28	11/7 - 11/10, 2011	NAI

Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability

OAI = Significant deviations from regulations. Data unreliable/Critical findings may affect data integrity.

Preliminary= The Establishment Inspection Report (EIR) has not been received and findings are based on preliminary communication with the field.

CLINICAL STUDY SITE INVESTIGATOR

1. Gary John Schiller, M.D./Study Protocol HSB-407/Site #026

Los, Angeles, CA

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.811, from November 29, 2011 to January 5, 2012.

For Study Protocol HSB-407, a total of 9 subjects were screened and enrolled, 2 subjects achieved remission and received allogenic transplants, and 7 completed the study. An audit of 9 enrolled subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. Limitations of inspection

None.

c. General observations/commentary

Source documents, for the nine subjects whose records were audited, were verified against the case report forms and NDA subject line listings. There was no under-reporting of serious adverse events.

In general, this clinical site appeared to be in compliance with Good Clinical Practices, although a two-observation Form FDA 483 (List of Inspectional Observations) was issued at the end of the inspection for some minor regulatory violations. These minor regulatory deficiencies were discussed with the review division medical team on January 18, 2012. The observations were not considered critical, and are considered unlikely to impact data integrity and reliability.

Selected minor regulatory observations of relevance included the following examples:

- An investigation was not conducted in accordance with the signed statement of the investigator. Specifically, a Form FDA 1572 was not updated in a timely manner that reflected inclusion of a study sub-investigator.
- For Subject #391, the first patient enrolled at the site, baseline weight instead of current weight was used in the calculation of body surface area for dose calculation for courses 2 and 3 of study medication. This resulted in doses of 3.2 mg/m² being administered for all three courses when the correct dose for course 2 would have been 3.1 mg/m² and for course 3 would have been 3.0 mg/m². This difference was not felt to be clinically significant by the principal investigator and subjects enrolled subsequently had the dose calculated correctly based on current (not baseline) weight.
- For Subject #392, there was an incorrectly reported absolute neutrophil count value of 0.79 x 10³ per µL on Treatment Course #1, Day #8, in the Case Report Form, instead of the correct absolute neutrophil count value of 0.4 x 10³ per µL. [Per Dr. Schiller's response to the issued Form FDA 483 on January 12, 2012, this value was subsequently corrected and no further clinical action was required at his investigative site.]

d. Data acceptability/reliability for consideration in the NDA review decision.

The regulatory deficiencies observed are minor and isolated in nature, and are not likely to significantly impact data acceptability. Data submitted by this clinical site appear acceptable for this specific indication.

2. Stuart Goldberg, M.D./Study Protocol HSB-407 /Site #193

Hackensack, NJ

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.811, from October 31 to November 4, 2011.

For HSB 407, a total of 5 subjects were enrolled and completed the study. An audit of 5 enrolled subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, CRFs, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. Limitations of inspection

None.

c. General observations/commentary

Source documents, for all of the subjects that were enrolled and randomized, were verified against the CRFs and NDA subject line listings. There was no under-reporting of serious adverse events noted.

This clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 was issued.

d. Data acceptability/reliability for consideration in the NDA review decision.

The data, in support of clinical efficacy and safety from this clinical site, appear acceptable for this specific indication.

3. Susan M. O'Brien, M.D./Study Protocol VSLI-06 /Site #001

Houston, TX

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.811, from November 7-10, 2011.

For VSLI-06, a total of 28 subjects were enrolled and completed the study. An audit of 28 enrolled subjects' records was conducted for informed consent.

The inspection evaluated the following documents for 8 study subjects: source records, screening and enrollment logs, CRFs, study drug accountability logs, study monitoring visits and correspondence. Sponsor-generated correspondence was also inspected.

b. Limitations of inspection

None.

c. General observations/commentary

Source documents, for 8 of the subjects that were enrolled and randomized, were verified against the CRFs and NDA subject line listings. There was no under-reporting of serious adverse events noted.

This clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 was issued.

d. Data acceptability/reliability for consideration in the NDA review decision.

The data, in support of clinical efficacy and safety from this clinical site, appear acceptable for this specific indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical investigator sites, two for Protocol HSB-07 and one for Protocol VSLI-06, were inspected in support of this application. No regulatory violations were noted for the Stuart Goldberg, M.D. and Susan O'Brien, M.D. sites audited. Although isolated regulatory deficiencies were noted at Dr. Gary Schiller's site, the findings appear unlikely to significantly impact data reliability.

Based on review of inspectional findings for these clinical investigators, the study data collected appear generally reliable in support of the requested indication.

{See appended electronic signature page}

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/s/

ANTHONY J ORENCIA
03/23/2012

JANICE K POHLMAN
03/26/2012

TEJASHRI S PUROHIT-SHETH
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