CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209401Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]		
NDA # 209401		
Proprietary Name: VYXEOS Established/Proper Name: daunorubicin and cytarabine Dosage Form: injection		Applicant: Celator Pharmaceuticals, Inc. (a Jazz Pharmaceuticals company) Agent for Applicant (if applicable): None
RPM: Wanda Nguyen, PharmD		Division: Division of Hematology Products
NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)		**For ALL 505(b)(2) applications, two months prior to EVERY action:** • **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.** • **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)** ☐ No changes ☐ New patent/exclusivity *(notify CDER OND IO)* Date of check: ***Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.***

❖ Actions	
• Proposed action • User Fee Goal Date is September 30, 2017	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

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

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only): combination anthracycline topoisomerase inhibitor and nucleoside metabolic inhibitor
(confirm chemical classification at time of approval)

☒ Fast Track
☒ Rolling Review
☒ Orphan drug designation
☒ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: CST SharePoint)

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other ASCO Burst
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Approval: 8/4/2017
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☒ Included 3/31/2017
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☐ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included 8/2/2017
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	Letter: Acceptable 6/21/2017 Review: 6/20/2017
❖ Labeling reviews *(indicate dates of reviews)*	RPM: 5/30/2017 DMEPA: 8/2/2017, 7/27/2017, and 7/17/2017 DMPP/PLT (DRISK): ☒ None OPDP: 7/14/17 SEALD: ☒ None CSS: ☒ None Product Quality: See Labeling section in 7/26/2017 in Integrated Quality Assessment Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	Filing 5/29/2017 505 (b)(2): cleared 7/26/2017
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☒ Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: orphan designation	Pediatric page 7/28/2017
❖ Breakthrough Therapy Designation	☐ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	Granted 5/17/2016
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	5/9/2016
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	8/2/2017, 8/1/2017, 7/28/2017 (2), 7/27/2017 (2), 7/25/2017 (3), 7/24/2017, 7/19/2017, 7/17/2017, 7/14/2017, 7/12/2017 (3), 7/10/2017, 7/7/2017 (2), 7/6/2017 (2), 7/5/2017, 6/20/2017 (2), 6/14/2017, 6/13/2017 (3), 6/9/2017, 6/6/2017, 6/5/2017, 6/1/2017(2), 5/30/2017 (2), 5/26/2017, 5/24/2017, 5/23/2017, 5/18/2017, 5/17/2017, 5/12/2017, 5/11/2017, 5/10/2017, 5/8/2017, 5/4/2017 (2), 5/1/2017 (2), 4/28/2017, 4/24/2017, 4/18/2017, 4/5/2017, 3/27/2017
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	Telecons: 7/31/2017, 7/21/2017, 7/20/2017, 7/12/2017, 7/6/2017, 6/29/2017, 6/8/2017, 5/31/2017, 5/25/2017, 5/17/2017
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	6/7/2016, 5/16/2016
• EOP2 meeting *(indicate date of mtg)*	5/25/2011, 7/29/2010
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	CMC 7/13/2016

❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	Multidisciplinary Review 8/3/2017 (Section 17)
Cross-Discipline Team Leader Review *(indicate date for each review)*	See 8/3/2017 Multidisciplinary Review (Section 1)
PMR/PMC Development Templates *(indicate total number)*	1
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	See 8/3/2017 Multidisciplinary Review (Section 2,3,4, and 7)
• Clinical review(s) *(indicate date for each review)*	See 8/3/2017 Multidisciplinary Review (Sections 2, 3, 4 and 7)
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See 8/3/2017 Multidisciplinary Review (Section 13.2)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	Division of Gastroenterology and Inborn Errors Products Review: 7/18/2017
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	Review: 5/3/2017 Letters: 4/24/2017; 12/20/2016 (2)
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	See 8/3/2017 Multidisciplinary Review (Section 7)
Statistical Team Leader Review(s) *(indicate date for each review)*	See 8/3/2017 Multidisciplinary Review (Section 7)
Statistical Review(s) *(indicate date for each review)*	See 8/3/2017 Multidisciplinary Review (Section 7)

[5] For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	See 8/3/2017 Multidisciplinary Review (Section 6)
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	See 8/3/2017 Multidisciplinary Review (Section 6)
Clinical Pharmacology review(s) *(indicate date for each review)*	See 8/3/2017 Multidisciplinary Review (Section 6) QT Studies Review: 6/23/2017
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	See 8/3/2017 Multidisciplinary Review (Section 5)
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	See 8/3/2017 Multidisciplinary Review (Section 5)
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (IQA) (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	Addendum to review 7/31/2017 Executive Summary 7/28/2017 Drug Substance 7/17/2017 Drug Product 7/26/2017 Labeling 7/26/2017 Process 7/24/2017 Facilities 7/28/2017 Biopharmaceutics 7/17/2017 Microbiology 6/30/2017
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☐ None

[6] Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See 7/28/2017 IQA Drug Product pages 1 and 49 of 50
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable (See 7/28/2017 IQA Facilities) ☐ Withhold recommendation ☐ Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☒ Done 8/3/17
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☒ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☐ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done
❖ Take Action Package (if in paper) down to Document Room for scanning within **two business days**	☒ Done

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/s/

WANDA D NGUYEN
08/04/2017

Nguyen, Wanda

From: Nguyen, Wanda
Sent: Wednesday, August 02, 2017 7:17 AM
To: 'Fojan Zamanian'; Robin Hume
Subject: NDA 209401 Vyxeos Label -- FDA comments
Attachments: GROUPED_.xpt; MUCOSITI.XPT; _301__LB.XPT; BILI_301.xpt; 8.2NDA209401CurrentLabelforReviewerEdits.docx

Follow Up Flag: Follow up
Flag Status: Flagged

Good Morning,

Please refer to the attached FDA labeling revisions to the prescribing information (PI) for NDA 209401 Vyxeos. Many of the labeling edits have been accepted. There are just a few edits made by the FDA team (with comments).

Please review the FDA revised labeling with your team by:

- Accepting remaining changes that you agree with
- If you need to make any edits, please do so only using track-changes (***do not reject any changes that the FDA proposed and do not delete any of the FDA's comments***)

After you have made any necessary changes, please send the revised tracked changes labeling document in Word only, via email to me before you make your official submission electronically. **Any edits made must be in tracked changes**.

Please send your reply no later than **Wednesday, 3PM, EST August 2, 2017**.

To Applicant:

Please find attached the revised PI as well as SAS transport files as requested for Agency's incidences of TEAEs during induction that differed from the applicant's (mucositis, hypertension, sepsis and fungal infection), as well as for grade ≥3 chemistry abnormalities that differed (hyponatremia, hypokalemia, and hyperbilirubinemia).

The Grouped file is a list of the Grouped terms with preferred terms within each group. The "mucositi" file is the file for FDA calculation of mucositis, hypertension, sepsis and fungal infection in each arm. The "301_LB" file is the file for calculation of grade 3 or greater hyponatremia and hypokalemia in each arm during induction (using any AVISIT term that contained "induction 1 (any day)" or "induction 2 (any day)," and ATOX1/ATOXG1. The "BILI_301" file is the file used for calculation of grade 3 or greater hyperbilirubinemia in each arm during induction, using ATOX2/ATOXG2.

Kindly confirm receipt of this correspondence.

Thanks,
Wanda

Wanda Nguyen, PharmD
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

10903 New Hampshire Avenue |Silver Spring, MD 20993
Wanda.Nguyen@fda.hhs.gov | 301-796-2808

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/s/

WANDA D NGUYEN
08/02/2017

24 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Nguyen, Wanda

From: Nguyen, Wanda
Sent: Friday, July 28, 2017 6:43 PM
To: 'Fojan Zamanian'
Cc: Robin Hume; Carioti, Theresa
Subject: NDA 209401 Vyxeos -- FDA Response to PMRs
Attachments: 7.28 NDA 209401Vyxeos -- PMRs_revised _clean.docx

Follow Up Flag: Follow up
Flag Status: Flagged

Good Evening,

Please refer to NDA 209401 Vyxeos (daunorubicin and cytarabine) liposome for injection.

We have reviewed your response to the PMRs, and FDA has accepted your timeline for the PMRs.

Please submit the agreed upon PMRs formally to the NDA by **12:00 PM (ET) on Monday, July 31, 2017.**

Thanks,
Wanda

Wanda Nguyen, PharmD
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

10903 New Hampshire Avenue |Silver Spring, MD 20993
Wanda.Nguyen@fda.hhs.gov | 301-796-2808

As per Agency's request please find below proposed revisions to the PMRs received on July 10, 2017 in tracked changes.

PMR-1

Characterize the nature, incidence and severity of infusion-related reactions in at least 50 patients treated with Vyxeos. The safety evaluation should include vital sign monitoring (temperature, pulse, respiratory rate, blood pressure, and oxygen saturation) at minimum immediately before initiation of the infusion, at 5 minutes, 15 minutes, 30 minutes, and at the end of the infusion, as well as for a prescribed period post-infusion. Characterize toxicities including changes in vital signs, anaphylaxis, respiratory distress, chills, back pain, flushing, chest-tightness and any other relevant signs or symptoms, as well as infusion interruptions and details (rate, time after initial interruption, outcome) regarding re-challenge, if applicable. Submit a summary of the analysis and datasets.

PMR/PMC Schedule Milestones:	Preliminary Protocol/ Analysis Plan Submission	November, 2017
	Final Protocol/ Analysis Plan Submission:	January, 2018
	Study Completion-	January, 2019
	Final Report Submission:	July, 2019

Applicant response:

Sponsor accepts all of FDA's proposed changes.

PMR-2

Conduct a clinical pharmacokinetic trial to determine an appropriate dose of Vyxeos to minimize toxicity in patients with moderate and severe renal impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled *Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	January, 2018
Trial Completion:	January, 2021
Final Report Submission:	June, 2021

Applicant response:

(b) (4)

(b) (4)

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/s/

WANDA D NGUYEN
07/31/2017

Nguyen, Wanda

From: Nguyen, Wanda
Sent: Tuesday, August 01, 2017 11:11 AM
To: 'Fojan Zamanian'; Robin Hume
Cc: Carioti, Theresa
Subject: NDA 209401 Vyxeos Label -- FDA Comments
Attachments: NDA209401CurrentLabelforReviewerEdits.docx

Good Morning,

Please refer to the attached FDA labeling revisions to the prescribing information (PI) for NDA 209401 Vyxeos. Many of the labeling edits have been accepted. There are just a few edits made by the FDA team (with comments).

Please review the FDA revised labeling with your team by:

- Accepting remaining changes that you agree with
- If you need to make any edits, please do so only using track-changes (***do not reject any changes that the FDA proposed and do not delete any of the FDA's comments***)

After you have made any necessary changes, please send the revised tracked changes labeling document in Word only, via email to me before you make your official submission electronically. **Any edits made must be in tracked changes**.

Please send your reply no later than **Wednesday, 10 AM EST August 2, 2017**.

Kindly confirm receipt of this correspondence.

Thanks,
Wanda

Wanda Nguyen, PharmD
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

10903 New Hampshire Avenue |Silver Spring, MD 20993
Wanda.Nguyen@fda.hhs.gov | 301-796-2808

U.S. FOOD & DRUG ADMINISTRATION

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/s/

WANDA D NGUYEN
08/02/2017

MEMORANDUM OF TELECONFERENCE

Teleconference Date: July 31, 2017

Application Number: NDA 209401
Product Name: Cytarabine and Daunorubicin Liposome for Injection
Sponsor/Applicant Name: Celator Pharmaceuticals (a Jazz Pharmaceuticals company)

Subject: Clinical Discussion Meeting – regarding Vyxeos, Prescribing Information

FDA Participants
Office of Hematology and Oncology Products (OHOP)/ Division of Hematology Products
Edvardas Kaminskas, MD, Deputy Director
Donna Przepiorka, MD, PhD, Clinical Team Leader
Aviva Krauss, MD, Clinical Reviewer
Virginia Kwitkowski, MS, RN, ACNP-BC, Clinical Team Lead
Wanda Nguyen, PharmD, Regulatory Project Manager
Theresa Carioti, MPH, Chief, Project Management Staff

Sponsor/Applicant Participants
Jazz Pharmaceuticals:
Karen Smith MD, PhD, Executive Vice President, R&D and CMO
Arthur Louie, MD, Vice President, Clinical Development
Stefan Faderl, MD, Senior Director, Clinical Development
Jin Zhu, PhD, Senior Director, Clinical Development
Kamalika Banerjee, MS, Senior Manager, Biostatistics
Charles LaPree, MS, Senior Vice President, Global Regulatory Affairs
Joanne Curley, Executive Director, Global Promotional Regulatory Affairs and Labeling
Robin Hume, MS, RAC, Senior Director, Global Regulatory Strategy
Fojan Zamanian, Director, Global Regulatory Strategy
Lawrence Mayer, PhD, Senior Vice President, Translational Research
Lisa Sellers, Associate Director Drug Safety
Scott Allender, MD, Director, Medical Director Drug Safety
Andreas Linkwitz, Senior Director Project Management
Joel Selcher, Executive Director Regulatory Affairs
Amber Cummins, Senior Director, Promotional Regulatory Affairs
Christy Wood, Senior Manager, Regulatory Affairs Labeling
Jamie McEntee, PharmD, Director, Regulatory Affairs Labeling
Samir Garg, Senior Director, Marketing
Dave Santos, Business Unit Head, Hematology Oncology
Mike Miller, Executive Vice President, US Commercial

1.0 BACKGROUND:

TheApplicant wanted to discuss specific issues relevant to the proposed labeling for Vyxeos, including: (1) the FDA's rationale for reversal for cytarabine and daunorubicin in product name and (2) inclusion of 'newly-diagnosed' in indication (b) (4)

2.0 DISCUSSION:

- FDA provisionally agreed to the new proposed language for hemorrhage in Warnings provided to the Agency on July 30, 2017 pending final review of the label.
- FDA provided rationale for the preferred order for Active agents "daunorubicin and cytarabine" to ensure daunorubicin prominence. The Applicant will accept reversal of the order of active agents.
- (b) (4) FDA noted initial approval indication can only be based on data submitted in the current NDA (b) (4) .
- The Applicant will send updated Label by 31 July 2017 3PM (EST) via email followed by formal submission to the NDA.

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

/s/

WANDA D NGUYEN
08/01/2017

Nguyen, Wanda

From: Nguyen, Wanda
Sent: Friday, July 28, 2017 9:30 AM
To: 'Fojan Zamanian'
Cc: Carioti, Theresa; Robin Hume
Subject: RE: NDA 209401 Vyxeos --FDA Response to Labeling Comments

Follow Up Flag: Follow up
Flag Status: Flagged

Good Morning Fojan,

Please refer to the attached FDA labeling revisions to the prescribing information (PI) for NDA 209401 VYXEOS.

We have the following response to your request for clarification attached below.
We are in agreement with your proposed approach except for #3.
That cohort should be anyone who received consolidation 1 whether or not they went to consolidation 2.
Please let know if you have any questions or concerns.

Thanks,
Wanda

From: Fojan Zamanian [mailto:Fojan.Zamanian@jazzpharma.com]
Sent: Friday, July 28, 2017 1:55 AM
To: Nguyen, Wanda
Cc: Carioti, Theresa; Fojan Zamanian; Robin Hume
Subject: RE: NDA 209401 Vyxeos --FDA Response to Labeling Comments
Importance: High

Dear Wanda,

The team have begun to review the label revisions from FDA and would like to confirm our understanding of the data request from FDA provided in Section 6.1 of the label, under laboratory abnormalities, Table 5. In FDA comment A25 the Agency has stated "Please fill in these blanks. Please also provide a time-to-event data file with the dates and days used to calculate the results". (see below extract from label):

Prolonged Cytopenias for Patients in Study 1

	(b) (4)

[a] Platelets < 50 Gi/L or neutrophils <0.5 Gi/L lasting past cycle day 42 in the absence of active leukemia.

Jazz Request for Clarification:

(b) (4)

[redacted]

If you can please confirm that the above algorithm is correct with the Agency request we will be able to move forward to provide the information as requested.

Kind regards,

Fojan Zamanian
Director, Regulatory Strategy

650.496.2795 (office)
(b) (6) *(mobile)*
fojan.zamanian@jazzpharma.com

From: Nguyen, Wanda [mailto:Wanda.Nguyen@fda.hhs.gov]
Sent: Thursday, July 27, 2017 12:10 PM
To: Robin Hume; Fojan Zamanian
Cc: Carioti, Theresa
Subject: NDA 209401 Vyxeos --FDA Response to Labeling Comments

Good Afternoon,

Please refer to the attached FDA labeling revisions to the prescribing information (PI) for NDA 209401 VYXEOS.

Please accept changes that you agree with in the label. Please ensure any new text, revisions, or updates to the label are made in tracked-changes only (do not reject any changes that the FDA proposed and do not delete any of the FDA's comments). Send your revised tracked changed USPI via email by **12 noon PM EST Monday, July 31, 2017** and then formally submit a copy to your NDA file.

Please note a separate email communication regarding review of the PMRs will be forthcoming.

Kindly confirm receipt of this correspondence.

Thanks,
Wanda

Wanda Nguyen, PharmD
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

10903 New Hampshire Avenue |Silver Spring, MD 20993
Wanda.Nguyen@fda.hhs.gov | 301-796-2808

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/s/

WANDA D NGUYEN
07/28/2017

Nguyen, Wanda

From: Nguyen, Wanda
Sent: Friday, July 28, 2017 6:43 PM
To: 'Fojan Zamanian'
Cc: Robin Hume; Carioti, Theresa
Subject: NDA 209401 Vyxeos -- FDA Response to PMRs
Attachments: 7.28 NDA 209401Vyxeos -- PMRs_revised _clean.docx

Follow Up Flag: Follow up
Flag Status: Flagged

Good Evening,

Please refer to NDA 209401 Vyxeos (daunorubicin and cytarabine) liposome for injection.

We have reviewed your response to the PMRs, and FDA has accepted your timeline for the PMRs.

Please submit the agreed upon PMRs formally to the NDA by **12:00 PM (ET) on Monday, July 31, 2017.**

Thanks,
Wanda

Wanda Nguyen, PharmD
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

10903 New Hampshire Avenue |Silver Spring, MD 20993
Wanda.Nguyen@fda.hhs.gov | 301-796-2808

As per Agency's request please find below proposed revisions to the PMRs received on July 10, 2017 in tracked changes.

PMR-1

Characterize the nature, incidence and severity of infusion-related reactions in at least 50 patients treated with Vyxeos. The safety evaluation should include vital sign monitoring (temperature, pulse, respiratory rate, blood pressure, and oxygen saturation) at minimum immediately before initiation of the infusion, at 5 minutes, 15 minutes, 30 minutes, and at the end of the infusion, as well as for a prescribed period post-infusion. Characterize toxicities including changes in vital signs, anaphylaxis, respiratory distress, chills, back pain, flushing, chest-tightness and any other relevant signs or symptoms, as well as infusion interruptions and details (rate, time after initial interruption, outcome) regarding re-challenge, if applicable. Submit a summary of the analysis and datasets.

PMR/PMC Schedule Milestones:	Preliminary Protocol/ Analysis Plan Submission	November, 2017
	Final Protocol/ Analysis Plan Submission:	January, 2018
	Study Completion-	January, 2019
	Final Report Submission:	July, 2019

Applicant response:

Sponsor accepts all of FDA's proposed changes.

PMR-2

Conduct a clinical pharmacokinetic trial to determine an appropriate dose of Vyxeos to minimize toxicity in patients with moderate and severe renal impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled *Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	January, 2018
Trial Completion:	January, 2021
Final Report Submission:	June, 2021

Applicant response:

(b) (4)


(b) (4)

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/s/

WANDA D NGUYEN
07/31/2017

Nguyen, Wanda

From: Nguyen, Wanda
Sent: Thursday, July 27, 2017 3:10 PM
To: 'Robin Hume'; 'Fojan Zamanian'
Cc: Carioti, Theresa
Subject: NDA 209401 Vyxeos --FDA Response to Labeling Comments
Attachments: 7.27NDA 209401 CurrentLabelforReviewerEdits.docx

Follow Up Flag: Follow up
Flag Status: Flagged

Good Afternoon,

Please refer to the attached FDA labeling revisions to the prescribing information (PI) for NDA 209401 VYXEOS.

Please accept changes that you agree with in the label. Please ensure any new text, revisions, or updates to the label are made in tracked-changes only (do not reject any changes that the FDA proposed and do not delete any of the FDA's comments). Send your revised tracked changed USPI via email by **12 noon PM EST Monday, July 31, 2017** and then formally submit a copy to your NDA file.

Please note a separate email communication regarding review of the PMRs will be forthcoming.

Kindly confirm receipt of this correspondence.

Thanks,
Wanda

Wanda Nguyen, PharmD
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

10903 New Hampshire Avenue |Silver Spring, MD 20993
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U.S. FOOD & DRUG ADMINISTRATION

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WANDA D NGUYEN
07/28/2017

Nguyen, Wanda

From: Nguyen, Wanda
Sent: Thursday, July 27, 2017 3:46 PM
To: 'Fojan Zamanian'; 'Robin Hume'
Cc: Carioti, Theresa
Subject: NDA 209401 CPX-351--FDA Information Request
Attachments: 5 Pack Carton Label.pdf

Good Afternoon Fojan,

Regarding your submission dated March 31, 2017 for NDA 209401 CPX-351, we have the following information requests. Please respond via email by **noon 12pm EST, Monday, July 31, 2017,** followed with a formal submission to the NDA.

Please see the carton labeling recommendations below:

A. Carton labeling
   1. "(b) (4)" to be changed to "interchange" to be consistent with the wording in the Prescribing Information in the boxed warning.

Thanks,
Wanda

Wanda Nguyen, PharmD
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

10903 New Hampshire Avenue |Silver Spring, MD 20993
Wanda.Nguyen@fda.hhs.gov | 301-796-2808

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/s/

WANDA D NGUYEN
07/31/2017

Nguyen, Wanda

From: Nguyen, Wanda
Sent: Tuesday, July 25, 2017 2:50 PM
To: 'Fojan Zamanian'; Robin Hume
Subject: NDA 209401 CPX-351 --FDA Labeling Recommendations

Follow Up Flag: Follow up
Flag Status: Flagged

Good Afternoon Fojan,

Regarding your submission dated March 31, 2017 for NDA 209401 CPX-351, we have the following information requests. Please respond via email followed with a formal submission to the NDA.

Please see the carton labeling recommendations below:

A. Carton labeling
    1. Include the statement in bold font on the side display panel, "**Carefully swirl the contents of the vial for 5 minutes.**" We recommend this revision to mitigate the risk of preparation errors and to bring prominence to this important information.

Thank you,
Wanda

Wanda Nguyen, PharmD
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

10903 New Hampshire Avenue |Silver Spring, MD 20993
Wanda.Nguyen@fda.hhs.gov | 301-796-2808

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/s/

WANDA D NGUYEN
07/28/2017

Nguyen, Wanda

From: Nguyen, Wanda
Sent: Tuesday, July 25, 2017 10:33 AM
To: 'Fojan Zamanian'; Robin Hume
Cc: Carioti, Theresa
Subject: NDA 209401 CPX-351 --FDA Information Request
Attachments: FDA_ADJU.XPT; FDA_ADJU1.xpt

Follow Up Flag: Follow up
Flag Status: Flagged

Good Morning Fojan,

Regarding your submission dated March 31, 2017 for NDA 209401 CPX-351, we have the following information requests. Please respond via email by **10 AM (ET) on Thursday, July 27, 2017**, followed with a formal submission to the NDA.

Information Request:

In your proposed revisions to the Vyxeos prescribing information (PI) submitted on 7/21/2017, you have made changes (b) (4) (b) (4) s. The numbers we included in these sections are based on FDA adjudication of root cause of death as well as reason for treatment discontinuation on Study 301 based on review of all available data (datasets, narratives, CRFs etc.) in the NDA submission. Attached please find SAS transport files with FDA adjudicated causes of death (FDA_ADJU1) and reasons for treatment discontinuation (FDA_ADJU). Please send in any information that would support your proposed changes to this section of the PI.

Thanks,
Wanda

Wanda Nguyen, PharmD
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

10903 New Hampshire Avenue |Silver Spring, MD 20993
Wanda.Nguyen@fda.hhs.gov | 301-796-2808

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/s/

WANDA D NGUYEN
07/28/2017

Bouie, Teshara

From: Kieran O'Donoghue <Kieran.ODonoghue@jazzpharma.com>
Sent: Tuesday, July 25, 2017 1:03 PM
To: Bouie, Teshara
Cc: Fojan Zamanian; Robin Hume; Nguyen, Wanda; Charles LaPree
Subject: RE: NDA 209401 - Confirmation of Issues Discussed

Hi Teshara,

Confirming receipt of this email and confirming that we are in agreement with the approach as discussed on the teleconference (July 25, 2017) and in your email below. Jazz will revalidate the lipid impurities test method, retest batches and submit the retest data to NDA 209401 via a General Correspondence as soon as the data is available.

Best
Kieran

From: Bouie, Teshara [mailto:Teshara.Bouie@fda.hhs.gov]
Sent: 25 July 2017 09:55
To: Kieran O'Donoghue
Cc: Fojan Zamanian; Robin Hume; Nguyen, Wanda
Subject: NDA 209401 - Confirmation of Issues Discussed

Hi Kieran,

As discussed by telephone on July 25, 2017 between Jazz Pharmaceuticals and the Office of Pharmaceutical Quality, regarding your method for lipid impurities, Jazz will revalidate, retest and submit the retest data to NDA 209401 via a General Correspondence as soon as the data is available.

Please confirm Jazz is in agreement with this approach.

Please confirm receipt of this email.

Regards,

Teshara G. Bouie, MSA, RAC, OTR/L
CDR, United States Public Health Service
Quality Assessment Lead (Acting)
FDA/CDER/OPQ/OPRO
Phone (301) 796-1649
Fax (301) 796-9749

FDA U.S. FOOD & DRUG ADMINISTRATION

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/s/

TESHARA G BOUIE
07/25/2017

Nguyen, Wanda

From: Nguyen, Wanda
Sent: Monday, July 24, 2017 11:09 AM
To: 'Fojan Zamanian'; Robin Hume
Cc: Carioti, Theresa
Subject: NDA 209401 Vyxeos (daunorubicin and cytarabine) liposome for injection --FDA comments on PMRs
Attachments: A20July2017 NDA 209401Vyxeos -- PMRs_revised.docx

Importance: High

Good Morning,

Please refer to NDA 209401 Vyxeos (daunorubicin and cytarabine) liposome for injection.

We have reviewed your response to the PMRs, and FDA has made some comments and edits to your proposed changes. Please review the attached and provide your response.

If you propose edits to the description, please make sure it's in tracked changes.

Upon mutual agreement of the PMRs, we ask you to submit both by email and officially a copy of the PMR/PMC studies/trials description to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial.

Please provide your response by **3:00 PM (ET) on Wednesday, July 26, 2017.**

Thanks,
Wanda

Wanda Nguyen, PharmD
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

10903 New Hampshire Avenue |Silver Spring, MD 20993
Wanda.Nguyen@fda.hhs.gov | 301-796-2808

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WANDA D NGUYEN
07/28/2017

MEMORANDUM OF TELECONFERENCE

Teleconference Date: July 20, 2017 and July 21, 2017

Application Number: NDA 209401
Product Name: Cytarabine and Daunorubicin Liposome for Injection
Sponsor/Applicant Name: Celator Pharmaceuticals (a Jazz Pharmaceuticals company)

Subject: Weekly CMC Review Team Status Meeting

FDA Participants
Office of Pharmaceutical Quality:
Anamitro Banerjee, Acting Branch Chief, OPQ/ONDP (7/20/2017 & 7/21/2017)
Paresma Patel, Drug Product Reviewer, OPQ/ONDP (7/20/2017 & 7/21/2017)
Christina Capacci-Daniel, Acting Quality Assessment Lead, OPQ/OPF/DIA (7/20/2017 & 7/21/2017)
Kumar Janoria, Process Reviewer, OPQ/OPF (7/20/2017)
David Bateman, Microbiology Reviewer, OPQ/OPF (7/20/2017)
Charles Jewell, Drug Substance Reviewer, OPQ/ONDP (7/20/2017)
Teshara G. Bouie, Acting Quality Assessment Lead, OPQ/OPRO (7/20/2017 & 7/21/2017)

Sponsor/Applicant Participants
Jazz Pharmaceuticals:
Anne Conneely, Associate Director, Technical Operations (7/20/2017)
Charles LaPree, Vice President, Global Regulatory Affairs (7/20/2017)
Les Mintzmyer, Vice President, Manufacturing and Technical Operations (7/20/2017 & 7/21/2017)
Kieran O'Donoghue, Director, Global Regulatory Affairs, CMC (7/20/2017 & 7/21/2017)
(b) (4) Consultant (7/20/2017)
Paul Tardi, Senior Director, Pre-formulation, Translational Research (7/20/2017 & 7/21/2017)
Sherwin Xie, Senior Director, Analytical R&D, Translational Research (7/20/2017 & 7/21/2017)
Fojan Zamanian, Director, Global Regulatory Affairs (7/20/2017)

1.0 BACKGROUND:

Purpose: Update review progress and discuss issues identified during the week.

2.0 DISCUSSION:

July 20, 2017:

Drug Product:

- Update on pending IRs ((b) (4) and updated specifications table): Jazz will submit their response on July 21, 2017 including a specification for (b) (4)

- The Agency informed Jazz that a CMC PMC concerning the lipid impurities method is forthcoming.
- Jazz plans to submit their revised content of labeling by 9:00 am EST July 21, 2017.

Jazz:

- Jazz questioned if the pending DMF IR response affects the review this NDA.
- Providing samples to the FDA St. Louis Lab has been an issue for Jazz. The Agency informed Jazz that typically the method validation process does not affect the NDA action.
- (b) (4) provided responses to the 483s on July 18, 2017. The Agency will contact (b) (4) if needed.

July 21, 2017:

- Jazz confirmed that their lipid impurities method revalidation is not scheduled to be completed until November 30, 2017.
- Per 21 CFR 210 and 211, material released for commercial use must be tested using validated methods.

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/s/

TESHARA G BOUIE
07/25/2017

Bouie, Teshara

From: Bouie, Teshara
Sent: Wednesday, July 19, 2017 12:58 PM
To: Kieran O'Donoghue (Kieran.ODonoghue@jazzpharma.com)
Cc: Fojan Zamanian (Fojan.Zamanian@jazzpharma.com); Robin Hume (Robin.Hume@jazzpharma.com); Nguyen, Wanda
Subject: NDA 209401 -Information Request

Hi Kieran,

The CMC team has the following requests:

- The levels of (b) (4) in your finished drug product surpass the control threshold of (b) (4)% of the PDE as defined by ICH Q3D. We also note that the levels of (b) (4) are significantly greater in commercial batches than in phase 3 clinical batches. Provide a specification test and adequately justified acceptance criteria to control for (b) (4) in your finished product specifications.
- Submit an updated specifications table to section 2.3.P.5 and section 3.2.P.5.1 that includes the current acceptance criteria for particle size, osmolality, DSPC assay, DSPG assay, in vitro release, and elemental impurities testing.

We request a response no later than COB July 21, 2017.

Please confirm receipt of this email.

Thanks,

Teshara G. Bouie, MSA, RAC, OTR/L
CDR, United States Public Health Service
Quality Assessment Lead (Acting)
FDA/CDER/OPQ/OPRO
Phone (301) 796-1649
Fax (301) 796-9749

Nguyen, Wanda

From: Nguyen, Wanda
Sent: Monday, July 17, 2017 10:06 AM
To: 'Fojan Zamanian'
Cc: Robin Hume; Bouie, Teshara; Kieran O'Donoghue
Subject: RE: NDA 209401 CPX-351 (Vyxeos) --FDA Information Request

Good Morning Fojan and Robin,

We are providing a response to the request for clarification that was included in the responses for carton/container comments.

Jazz Question 4: *We noticed inconsistencies throughout the comments regarding where "liposome" should be placed in relation to the non-proprietary name. In accordance with FDA's Guidance for Industry, Liposome Drug Products, we recommend the nonproprietary name include terminology to express that the product is a liposome. Accordingly, we recommend the* (b) (4) *Does the Agency agree?*

Agency Response: No, the Agency recommends that liposome be placed directly after the parentheses to indicate that both drug substances are encapsulated. For example, "VYXEOS (daunorubicin and cytarabine) liposome for injection."

We also have the following additional comment, and request a response by Wednesday, **July 19th**:
• We recommend the Applicant revise the container label and carton labeling from "For Intravenous (b) (4) Only" to "For Intravenous **Infusion** Only".

Thanks,
Wanda

From: Fojan Zamanian [mailto:Fojan.Zamanian@jazzpharma.com]
Sent: Thursday, July 13, 2017 6:54 PM
To: Nguyen, Wanda
Cc: Robin Hume; Bouie, Teshara; Kieran O'Donoghue; Fojan Zamanian
Subject: RE: NDA 209401 CPX-351 (Vyxeos) --FDA Information Request

Dear Wanda,

I writing to inform you that today 13 July 2017 we submitted to the NDA (SN0037) our responses to information request received 7 July 2017. Please find attached a courtesy copy of the submission.

Should you have any questions or comments, please do not hesitate to contact me.

Kind regards,

Fojan Zamanian
Director, Regulatory Strategy
(b) (6) *(mobile)*
fojan.zamanian@jazzpharma.com

Jazz Pharmaceuticals
Innovation that performs

From: Nguyen, Wanda [mailto:Wanda.Nguyen@fda.hhs.gov]
Sent: Friday, July 07, 2017 12:54 PM
To: Fojan Zamanian; Robin Hume
Subject: NDA 209401 CPX-351 (Vyxeos) --FDA Information Request

Good Morning Fojan,

Regarding your submission dated March 31, 2017 for NDA 209401 CPX-351, we have the following information requests. Please respond via email by **5 PM (ET) on Thursday July 13, 2017**, followed with a formal submission to the NDA.

A. Container Label and Carton Labeling Comments:

1. Reverse the order of drug substances to read "daunorubicin and cytarabine" throughout the container label and carton labeling. Refer to daunorubicin first throughout all labeling including: the principal display panel (PDP), "do not substitute" warning banner, side panel, reconstitution instructions, and ingredients listing.
2. Revise the established name from, "daunorubicin" to "DAUNOrubicin" to ensure consistency with the Office of Generic Drugs list of Tallman letters[1].
3. Remove the (b) (4) and the (b) (4) on the strength presentations and ingredients listing from the container label and carton labeling as it is not necessary for your drug product.
4. Move the route of administration statement "FOR INTRAVENOUS (b) (4) ONLY" right underneath the strength presentation.
5. Bold the statement, "Discard unused portion" on the principal display panel to bring prominence to important handling information.

B. Container label

1. If space will allow, move the reconstitution and dilution statement to the principal display panel.

C. Carton Labeling Comments:

1. Revise the ingredients listing on the back panel of the carton labeling to be consistent with the PI. For example: "Each vial contains 44 mg daunorubicin and 100 mg cytarabine, and the following inactive ingredients: distearoylphosphatidylcholine 454 mg, distearoylphosphatidylglycerol 132 mg, cholesterol HP 32 mg, copper gluconate 100 mg, triethanolamine 4 mg, and sucrose 2054 mg."
2. Display the net quantity and sterility statement (i.e. Contains 2 Sterile Single-dose vials) on the PDP instead of the side panel.
3. Include the statement, "Rx only" on the PDP as required by Section 503(b)(4)(A) of the Federal Food, Drug and Cosmetic Act.
4. Include the statement "Must be Reconstituted, then diluted" on the PDP. We recommend this to minimize the risk of administering the product as an intravenous bolus.

5. Increase the font size of the warning statement, "Do not [redacted] (b) (4) with other drugs containing cytarabine or DAUNOrubicin" to bring prominence to this important information.

Thanks,
Wanda

Wanda Nguyen, PharmD
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

10903 New Hampshire Avenue |Silver Spring, MD 20993
Wanda.Nguyen@fda.hhs.gov | 301-796-2808

[1] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013, lines [479-492]. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

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WANDA D NGUYEN
07/28/2017

From:	Bouie, Teshara
Sent:	Friday, July 14, 2017 7:26 AM
To:	Kieran O'Donoghue (Kieran.ODonoghue@jazzpharma.com)
Cc:	Nguyen, Wanda; Fojan Zamanian (Fojan.Zamanian@jazzpharma.com); Robin Hume (Robin.Hume@jazzpharma.com)
Subject:	NDA 209401 - Information Request

Hi Kieran,

The CMC team requests the following:

Please update the module 3.2.P.3.4 CONTROLS OF CRITICAL STEPS AND INTERMEDIATES to include additional IPCs as discussed in your response dated 05/19/2017 and 06/07/2017.

We request a response by 7/18/2017.

Please confirm receipt of this email.

Thanks,

Teshara G. Bouie, MSA, RAC, OTR/L
CDR, United States Public Health Service
Quality Assessment Lead (Acting)
FDA/CDER/OPQ/OPRO
Phone (301) 796-1649
Fax (301) 796-9749

FDA U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF TELECONFERENCE

Teleconference Date: July 12, 2017

Application Number: NDA 209401
Product Name: Cytarabine and Daunorubicin Liposome for Injection
Sponsor/Applicant Name: Celator Pharmaceuticals (a Jazz Pharmaceuticals company)

Subject: Weekly CMC Review Team Status Meeting

FDA Participants
Office of Pharmaceutical Quality:
Anamitro Banerjee, Acting Branch Chief, OPQ/ONDP
Paresma Patel, Drug Product Reviewer, OPQ/ONDP
Christina Capacci-Daniel, Acting Quality Assessment Lead, OPQ/OPF/DIA
Maotang Zhou, Process Reviewer, OPQ/OPF
David Bateman, Microbiology Reviewer, OPQ/OPF
Charles Jewell, Drug Substance Reviewer, OPQ/ONDP
Teshara G. Bouie, Acting Quality Assessment Lead, OPQ/OPRO

Sponsor/Applicant Participants
Jazz Pharmaceuticals:
Robin Hume, Senior Director, Global Regulatory Affairs
Charles LaPree, Vice President, Global Regulatory Affairs
Barry Liboiron, Director, Biophysical Characterization & Advanced Solutions, Translational Research
Les Mintzmyer, Vice President, Manufacturing and Technical Operations
Enda Noone, Associate Director, Quality Control
Kieran O'Donoghue, Director, Global Regulatory Affairs, CMC
(b) (4) Consultant
Paul Tardi, Senior Director, Pre-formulation, Translational Research
Sherwin Xie, Senior Director, Analytical R&D, Translational Research

1.0 BACKGROUND:

Purpose: Update review progress and discuss issues identified during the week.

2.0 DISCUSSION:

Drug Product:

- Heavy Metals Testing: Jazz stated data for (b) (4) levels are higher than expected and therefore they are performing confirmatory testing at their contract laboratory. Current data shows levels that exceed PDE by approximately (b) (4) times. Jazz anticipates submitting the results by Friday 7/14 but will confirm the timeframe by COB 7/13.

Process:

- Jazz plans to respond to the pending information request by 7/13.

Labeling:

- Updated carton/containers labels will be submitted by 7/14.
- Jazz plans to contact DHP requesting an extension for the submission of the full Prescribing Information.

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/s/

TESHARA G BOUIE
07/13/2017

From: Bouie, Teshara
Sent: Wednesday, July 12, 2017 3:49 PM
To: Kieran O'Donoghue (Kieran.ODonoghue@jazzpharma.com)
Cc: Fojan Zamanian (Fojan.Zamanian@jazzpharma.com); Robin Hume (Robin.Hume@jazzpharma.com); Nguyen, Wanda
Subject: NDA 209401 - CMC Comment

Hi Kieran,

The CMC team has the following comment:

- We recommend that Jazz test the phase 3 clinical batches 1E003 and 4D007 for (b) (4) impurities in addition to the PPQ batches.

Regards,

Teshara G. Bouie, MSA, RAC, OTR/L
CDR, United States Public Health Service
Quality Assessment Lead (Acting)
FDA/CDER/OPQ/OPRO
Phone (301) 796-1649
Fax (301) 796-9748

FDA U.S. FOOD & DRUG ADMINISTRATION

Nguyen, Wanda

From: Nguyen, Wanda
Sent: Wednesday, July 12, 2017 6:49 AM
To: 'Fojan Zamanian'; 'Robin Hume'
Subject: NDA 209401 CPX-351 (Vyxeos)--FDA Information Request

Follow Up Flag: Follow up
Flag Status: Flagged

Good Morning,

Regarding your submission dated March 31, 2017 for NDA 209401 CPX-351, we have the following information requests. Please respond via email by **5 PM (ET) on Friday, July 14, 2017**, followed with a formal submission to the NDA.

Please provide a justification for your reliance on the reference listed drugs DaunoXome and DepoCyt in your NDA. The justification should include the scientific basis for relying on studies for those drugs, and how you have established the bridge from Vyxeos to these drugs. For further detail, please refer to the Agency response to Question 6 in the minutes of the pre-NDA meeting held on May 16, 2016.

Thanks,
Wanda

Wanda Nguyen, PharmD
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

10903 New Hampshire Avenue |Silver Spring, MD 20993
Wanda.Nguyen@fda.hhs.gov | 301-796-2808

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/s/

WANDA D NGUYEN
07/28/2017

Nguyen, Wanda

From: Nguyen, Wanda
Sent: Wednesday, July 12, 2017 4:39 PM
To: 'Fojan Zamanian'
Cc: Carioti, Theresa; Robin Hume; Kieran O'Donoghue
Subject: RE: NDA 209401 Vyxeos (daunorubicin and cytarabine) liposome for injection--Labeling comments
Attachments: FDA adjudication of CR by USUBJID and arm.xlsx

Good Evening Fojan and Robin,

Attached is the excel file with the FDA adjudicated response variable.
Below is the Agency's response to your clarification request.
Please let me know if we have answered all your questions.

Response:

Question 1: The common adverse reactions in the highlights and section 6.1 summarize those seen during the combined treatment periods.

Question 2: Please send in your proposed changes for section 8.5 with your revised label.

Question 3: FDA assessed a patient to have achieved CR when the collective data from the ADSL and ADLB datasets as well as the CRFs and independent hematopathologist comments demonstrated the following:
a BM during the induction period(s) showed <5% blasts, and peripheral neutrophil and platelets counts returned to >1000/mcL and 100,000/mcL , respectively within 14 days of the remission BM.
See attached file for FDA adjudicated CR responses. The blank cells under either column represent patients who were not assessed to have achieved CR.

Question 4: Please send in your proposed changes for the nonproprietary name with your revised label.

Thanks,
Wanda

From: Fojan Zamanian [mailto:Fojan.Zamanian@jazzpharma.com]
Sent: Wednesday, July 12, 2017 1:19 PM
To: Nguyen, Wanda
Cc: Carioti, Theresa; Robin Hume; Kieran O'Donoghue
Subject: Re: NDA 209401 Vyxeos (daunorubicin and cytarabine) liposome for injection--Labeling comments

Dear Wanda,

Following up to see when we can anticipate a response on the request for clarification.

Kind regards,

Fojan

Sent from my iPhone

On Jul 11, 2017, at 8:25 PM, Fojan Zamanian <Fojan.Zamanian@jazzpharma.com> wrote:

Dear Wanda,

In reviewing the Label you sent on Friday our team has identified four questions for which we seek clarification. Please see attached document which includes outlines our questions.

This clarification is needed in order for us to move forward with our analysis. We appreciate your confirmation of the request and prompt reply.

Also, I wanted to provide a quick update. As per Agency's request on 13 July 2017 we plan to provide a response to the FDA labeling revisions to the prescribing information (PI) and container/ carton label comments received on Friday 7 July 2017. However, there are several new analyses that need to be conducted in order to produce the data requested and/or verify changes to data made by FDA. We have noted those places within the response document respectively. We would like clarification on how to submit the revised response once those data are available at the end of next week 21 July 2017.

Kind regards,

Fojan Zamanian
Director, Regulatory Strategy

650.496.2795 (office)
(b) (6) *(mobile)*
fojan.zamanian@jazzpharma.com

<image002.jpg>

From: Nguyen, Wanda [mailto:Wanda.Nguyen@fda.hhs.gov]
Sent: Friday, July 07, 2017 11:24 AM
To: Robin Hume; Fojan Zamanian
Cc: Carioti, Theresa
Subject: NDA 209401 Vyxeos (daunorubicin and cytarabine) liposome for injection--Labeling comments

Good Afternoon,

Please refer to the attached FDA labeling revisions to the prescribing information (PI) for NDA 209401 Vyxeos (daunorubicin and cytarabine) liposome for injection.

Please review the FDA revised labeling with your team by:

- Accepting changes that you agree with
- Making any edits that you do not agree with using track-changes only (***do not reject any changes that the FDA proposed and do not delete any of the FDA's comments, if you have revised text, please include description in a comment***)

After you have made any necessary changes, please send the revised tracked changes labeling documents via email to me before you make your official submission electronically. **Any edits made must be in tracked changes**.

Please submit your responses to the labeling comments by **Thursday, July 13, 2017, Noon EST**.

Kindly confirm receipt of this correspondence.

Thanks,
Wanda

Wanda Nguyen, PharmD
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

10903 New Hampshire Avenue |Silver Spring, MD 20993
Wanda.Nguyen@fda.hhs.gov | 301-796-2808

<11July2017 Vyxeos label clarification question finalized.pdf>

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/s/

WANDA D NGUYEN
07/28/2017

Nguyen, Wanda

From: Nguyen, Wanda
Sent: Monday, July 10, 2017 10:11 AM
To: 'Robin Hume'; 'Fojan Zamanian'
Subject: NDA 209401 Vyxeos (daunorubicin and cytarabine) liposome for injection--PMR
Attachments: NDA 209401Vyxeos -- PMRs.docx

Good Morning,

Please refer to NDA 209401 Vyxeos (daunorubicin and cytarabine) liposome for injection.

We are also providing you with proposed post marketing studies. Please review the attached FDA proposed PMR/PMCs and provide your response. If you propose edits to the description, please make sure it's in tracked changes.

Upon mutual agreement of the PMR/PMCs, we ask you to submit both by email and officially a copy of the PMR/PMC studies/trials description to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial.

Please provide your response by **5PM (ET), Thursday, July 13, 2017.**

Thanks,
Wanda

Wanda Nguyen, PharmD
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

10903 New Hampshire Avenue |Silver Spring, MD 20993
Wanda.Nguyen@fda.hhs.gov | 301-796-2808

As we continue our review of your NDA, our normal policy is to consider labeling and post-marketing studies at this time, so that they can be completed in advance of any action date. We have determined that the following clinical trials are necessary as post-marketing requirements (PMRs) based on the data available to date. These brief summaries are intended to describe the main trial characteristics of interest. Please supplement and comment to clarify mutually acceptable descriptions of the key trial elements. We are available to discuss by T-con if needed.

Upon mutual agreement for the content and timing of the PMR, submit to us, both by email and officially, the full text and the timeline for the PMR study/trial you will perform with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial. Milestone times only need a month and year. For milestone calculations purposes only, assume that an approval occurs on the PDUFA date.

Note that the "Final Protocol Submission" date is the date on (or before) which you submit a complete protocol that has already received full concurrence by FDA. We suggest that you consider realistic milestone times.

Final PMR designation numbers will be assigned later.

PMR-1

Characterize the nature, incidence and severity of infusion-related reactions in at least 50 patients treated with Vyxeos. Include in the safety evaluation vital sign monitoring, including temperature, pulse, respiratory rate, blood pressure, and oxygen saturation, at minimum immediately before initiation of the infusion, at 5 minutes, 15 minutes, 30 minutes, and at the end of the infusion, as well as for a prescribed period post-infusion. Characterize toxicities including changes in vital signs, anaphylaxis, respiratory distress, chills, back pain, flushing, chest-tightness and any other relevant signs or symptoms, as well as infusion interruptions and details (rate, time after initial interruption, outcome) regarding re-challenge, if applicable. Submit a summary of the analysis and datasets.

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

PMR-2

Conduct a clinical pharmacokinetic trial to determine an appropriate dose of Vyxeos to minimize toxicity in patients with moderate and severe renal impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled *Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	MM/YYYY
	Final Report Submission:	MM/YYYY

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/s/

WANDA D NGUYEN
07/28/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209401

INFORMATION REQUEST

Celator Pharmaceuticals, Inc. (a Jazz Pharmaceuticals company)
Attention: Kieran O'Donoghue
Director, Regulatory Affairs CMC
3180 Porter Drive
Palo Alto, CA 94304

Dear Mr. O'Donoghue:

Please refer to your New Drug Application (NDA) dated March 31, 2017, received March 31, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cytarabine and Daunorubicin Liposome for Injection.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response, **no later than July 13, 2017**, in order to continue our evaluation of your NDA.

1. [redacted] (b) (4) . Demonstrate that the procedure in the PI (Section 2.6) will yield a reconstituted solution in the vial that meets key quality attributes including: appearance, particulate matter, and particle size. Perform these studies on drug product immediately after reconstitution and on reconstituted drug product that has been stored at 2-8 °C for up to 4 hours.

2. Release testing and stability testing should be performed using units that represent the product that you intend to distribute for commercial use. Update the drug product release methods to clarify if there are any cake appearance criteria for release or stability testing. Additionally, demonstrate that vials with [redacted] (b) (4) lyophilized cakes meet key quality attributes including: reconstitution time, particulate matter, particle size, and in vitro release. Alternatively, include a specification test and acceptance criteria for appearance that prevents vials with [redacted] (b) (4) lyophilized cake from being released.

3. You indicate that the only allowable [redacted] (b) (4) . However batch 6K001, which

was used to support this [redacted] failed to meet the finished product acceptance criterion. Provide data to support this [redacted] for batches which pass the release specifications or revise the [redacted] following 21 CFR 211.115.

4. Provide the [redacted] of manufacturing process. Any changes made to manufacturing process [redacted] should be justified or repeated to [redacted]

If you have any questions, please contact me, at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

Teshara G. Bouie, MSA, RAC, OTR/L
CDR, USPHS, Quality Assessment Lead (Acting)
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Teshara Bouie

Digitally signed by Teshara Bouie
Date: 7/06/2017 04:12:54PM
GUID: 508da7230002a24fd4abdd8018af2a08

Reference ID: 4138665

Nguyen, Wanda

From: Nguyen, Wanda
Sent: Friday, July 07, 2017 2:24 PM
To: 'Robin Hume'; Fojan Zamanian
Cc: Carioti, Theresa
Subject: NDA 209401 Vyxeos (daunorubicin and cytarabine) liposome for injection--Labeling comments
Attachments: A7.7NDA209401CurrentLabelforReviewerEdits.docx

Good Afternoon,

Please refer to the attached FDA labeling revisions to the prescribing information (PI) for NDA 209401 Vyxeos (daunorubicin and cytarabine) liposome for injection.

Please review the FDA revised labeling with your team by:

- Accepting changes that you agree with
- Making any edits that you do not agree with using track-changes only (***do not reject any changes that the FDA proposed and do not delete any of the FDA's comments, if you have revised text, please include description in a comment***)

After you have made any necessary changes, please send the revised tracked changes labeling documents via email to me before you make your official submission electronically. **Any edits made must be in tracked changes**.

Please submit your responses to the labeling comments by **Thursday, July 13, 2017, Noon EST**.

Kindly confirm receipt of this correspondence.

Thanks,
Wanda

Wanda Nguyen, PharmD
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

10903 New Hampshire Avenue |Silver Spring, MD 20993
Wanda.Nguyen@fda.hhs.gov | 301-796-2808

U.S. FOOD & DRUG ADMINISTRATION

40 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

As we continue our review of your NDA, our normal policy is to consider labeling and post-marketing studies at this time, so that they can be completed in advance of any action date. We have determined that the following clinical trials are necessary as post-marketing requirements (PMRs) based on the data available to date. These brief summaries are intended to describe the main trial characteristics of interest. Please supplement and comment to clarify mutually acceptable descriptions of the key trial elements. We are available to discuss by T-con if needed.

Upon mutual agreement for the content and timing of the PMR, submit to us, both by email and officially, the full text and the timeline for the PMR study/trial you will perform with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial. Milestone times only need a month and year. For milestone calculations purposes only, assume that an approval occurs on the PDUFA date.

Note that the "Final Protocol Submission" date is the date on (or before) which you submit a complete protocol that has already received full concurrence by FDA. We suggest that you consider realistic milestone times.

Final PMR designation numbers will be assigned later.

PMR-1

Characterize the nature, incidence and severity of infusion-related reactions in at least 50 patients treated with Vyxeos. Include in the safety evaluation vital sign monitoring, including temperature, pulse, respiratory rate, blood pressure, and oxygen saturation, at minimum immediately before initiation of the infusion, at 5 minutes, 15 minutes, 30 minutes, and at the end of the infusion, as well as for a prescribed period post-infusion. Characterize toxicities including changes in vital signs, anaphylaxis, respiratory distress, chills, back pain, flushing, chest-tightness and any other relevant signs or symptoms, as well as infusion interruptions and details (rate, time after initial interruption, outcome) regarding re-challenge, if applicable. Submit a summary of the analysis and datasets.

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

PMR-2

Conduct a clinical pharmacokinetic trial to determine an appropriate dose of Vyxeos to minimize toxicity in patients with moderate and severe renal impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled *Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	MM/YYYY
	Final Report Submission:	MM/YYYY

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/s/

WANDA D NGUYEN
07/10/2017

Nguyen, Wanda

From: Nguyen, Wanda
Sent: Friday, July 07, 2017 3:54 PM
To: Fojan Zamanian; 'Robin Hume'
Subject: NDA 209401 CPX-351 (Vyxeos) --FDA Information Request

Follow Up Flag: Follow up
Flag Status: Flagged

Good Morning Fojan,

Regarding your submission dated March 31, 2017 for NDA 209401 CPX-351, we have the following information requests. Please respond via email by **5 PM (ET) on Thursday July 13, 2017**, followed with a formal submission to the NDA.

A. Container Label and Carton Labeling Comments:

1. Reverse the order of drug substances to read "daunorubicin and cytarabine" throughout the container label and carton labeling. Refer to daunorubicin first throughout all labeling including: the principal display panel (PDP), "do not substitute" warning banner, side panel, reconstitution instructions, and ingredients listing.
2. Revise the established name from, "daunorubicin" to "DAUNOrubicin" to ensure consistency with the Office of Generic Drugs list of Tallman letters[1].
3. Remove the (b) (4) and the (b) (4) on the strength presentations and ingredients listing from the container label and carton labeling as it is not necessary for your drug product.
4. Move the route of administration statement "FOR INTRAVENOUS (b) (4) ONLY" right underneath the strength presentation.
5. Bold the statement, "Discard unused portion" on the principal display panel to bring prominence to important handling information.

B. Container label

1. If space will allow, move the reconstitution and dilution statement to the principal display panel.

C. Carton Labeling Comments:

1. Revise the ingredients listing on the back panel of the carton labeling to be consistent with the PI. For example: "Each vial contains 44 mg daunorubicin and 100 mg cytarabine, and the following inactive ingredients: distearoylphosphatidylcholine 454 mg, distearoylphosphatidylglycerol 132 mg, cholesterol HP 32 mg, copper gluconate 100 mg, triethanolamine 4 mg, and sucrose 2054 mg."
2. Display the net quantity and sterility statement (i.e. Contains 2 Sterile Single-dose vials) on the PDP instead of the side panel.
3. Include the statement, "Rx only" on the PDP as required by Section 503(b)(4)(A) of the Federal Food, Drug and Cosmetic Act.
4. Include the statement "Must be Reconstituted, then diluted" on the PDP. We recommend this to minimize the risk of administering the product as an intravenous bolus.
5. Increase the font size of the warning statement, "Do not (b) (4) with other drugs containing cytarabine or DAUNOrubicin" to bring prominence to this important information.

Thanks,
Wanda

Wanda Nguyen, PharmD
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

10903 New Hampshire Avenue |Silver Spring, MD 20993
Wanda.Nguyen@fda.hhs.gov | 301-796-2808

[1] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013, lines [479-492]. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

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/s/

WANDA D NGUYEN
07/10/2017

MEMORANDUM OF TELECONFERENCE

Teleconference Date: July 6, 2017

Application Number: NDA 209401
Product Name: Cytarabine and Daunorubicin Liposome for Injection
Sponsor/Applicant Name: Celator Pharmaceuticals (a Jazz Pharmaceuticals company)

Subject: Weekly CMC Review Team Status Meeting

FDA Participants
Office of Pharmaceutical Quality:
Anamitro Banerjee, Acting Branch Chief, OPQ/ONDP
Paresma Patel, Drug Product Reviewer, OPQ/ONDP
Christina Capacci-Daniel, Acting Quality Assessment Lead, OPQ/OPF/DIA
Kumar Janoria, Process Reviewer, OPQ/OPF
David Bateman, Microbiology Reviewer, OPQ/OPF
Charles Jewell, Drug Substance Reviewer, OPQ/ONDP
Teshara G. Bouie, Acting Quality Assessment Lead, OPQ/OPRO

Sponsor/Applicant Participants
Jazz Pharmaceuticals:
Robin Hume, Senior Director, Global Regulatory Affairs
Les Mintzmyer, Vice President, Manufacturing and Technical Operations
Enda Noone, Associate Director, Quality Control
Kieran O'Donoghue, Director, Global Regulatory Affairs, CMC
(b) (4) Consultant
Paul Tardi, Senior Director, Pre-formulation, Translational Research
Sherwin Xie, Senior Director, Analytical R&D, Translational Research

1.0 BACKGROUND:

Purpose: Update review progress and discuss issues identified during the week.

2.0 DISCUSSION:

Drug Product:

- CMC carton and container comments along with DMEPA comments will be sent out next week.
- Heavy metals testing submission is requested sooner than the promised date of 7/14. Jazz will try to expedite but testing is ongoing and 7/14 may be earliest submission date.

Process:

- Additional Information requests were sent to Jazz on July 6, 2017 (see panorama).

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/s/

TESHARA G BOUIE
07/07/2017

From: Bouie, Teshara
Sent: Thursday, July 06, 2017 10:50 AM
To: 'Kieran O'Donoghue'
Cc: Robin Hume; Fojan Zamanian; Nguyen, Wanda
Subject: RE: CPX-351 Liposome for Injection - Proposed IVR Acceptance Criteria (Follow up to June 22 CMC Telecon)

Hi Kieran,

Your counter-proposed IVR acceptance criteria for daunorubicin and cytarabine (as shown below) are deemed acceptable for the routine QC testing of the VYXEOS Liposome Injection. Revise the Finished Product Specifications Table and other pertinent documents in the NDA accordingly.

1 hour: NMT (b) (4)%
6 hours: (b) (4)%
72 hours: NLT (b) (4)%

Thanks,

Teshara G. Bouie

From: Kieran O'Donoghue [mailto:Kieran.ODonoghue@jazzpharma.com]
Sent: Wednesday, July 05, 2017 1:52 PM
To: Bouie, Teshara
Cc: Robin Hume; Fojan Zamanian; Nguyen, Wanda
Subject: RE: CPX-351 Liposome for Injection - Proposed IVR Acceptance Criteria (Follow up to June 22 CMC Telecon)

Hi Teshara,

Hope you are well. Please find attached our response to the question on the use of (b) (4) of the IVR profile. We would like to discuss this and any additional information requests that we can expect to receive during tomorrows CMC teleconference.

Best
Kieran

From: Kieran O'Donoghue
Sent: 30 June 2017 19:06
To: Teshara.Bouie@fda.hhs.gov
Cc: Robin Hume; Fojan Zamanian; Wanda.Nguyen@fda.hhs.gov
Subject: RE: CPX-351 Liposome for Injection - Proposed IVR Acceptance Criteria (Follow up to June 22 CMC Telecon)

Hi Teshara,

Please find attached our response to the additional request from the biopharmaceutics team received yesterday (June 29, 2017) and discussed at yesterdays CMC teleconference. We will follow up with the Agency by next Wednesday on the (b) (4).

Best

Kieran

From: Bouie, Teshara [mailto:Teshara.Bouie@fda.hhs.gov]
Sent: 29 June 2017 16:24
To: Kieran O'Donoghue
Cc: Robin Hume; Fojan Zamanian; Nguyen, Wanda
Subject: RE: CPX-351 Liposome for Injection - Proposed IVR Acceptance Criteria (Follow up to June 22 CMC Telecon)

Hi Kieran,

Thank you for your response. The biopharmaceutics team has the following additional request:

- To facilitate our review of the counter-proposed IVR acceptance range ((b) (4)%) at 6 hours, and the final specification time point (72 hours) provide additional justification in terms of ability to reject "failed" commercial scale Batch # 6K001.
  In deriving the predicted dissolution data at (b) (4) hours, we suggest using (b) (4)

Please confirm receipt of this email.

Thanks,

Teshara G. Bouie

From: Kieran O'Donoghue [mailto:Kieran.ODonoghue@jazzpharma.com]
Sent: Wednesday, June 28, 2017 12:29 PM
To: Bouie, Teshara
Cc: Robin Hume; Fojan Zamanian; Rivera, Luz E (CDER)
Subject: CPX-351 Liposome for Injection - Proposed IVR Acceptance Criteria (Follow up to June 22 CMC Telecon)

Hi Teshara,

I hope this email finds you well. In accordance with last weeks CMC teleconference (June 22, 2017), please find attached our response to the proposed IVR acceptance criteria. We would like to discuss this proposal at tomorrows CMC teleconference in addition to the 483 observations resulting from the recently completed PAI at (b) (4). Can you please let me know if the Agency have any topics for discussion at tomorrows call.

Best
Kieran

Kieran O'Donoghue
Director - CMC Regulatory Affairs
Jazz Pharmaceuticals
Phone: +353-1-634-7841
Cell: (b) (6)
mailto:kieran.odonoghue@Jazzpharma.com

Follow-up FDA Comment regarding response to Biopharmaceutics Question #2 (IVR acceptance criteria) of FDA Information Request #5 received June 09, 2017:

We acknowledge your agreement with the use of one set of IVR acceptance criteria for both cytarabine and daunorubicin, as well as FDA's recommended acceptance criterion for the first specification time point (NMT (b) (4)% at 1 hour).
Note that FDA does not agree with your overall justification for IVR acceptance criteria setting which is based on (b) (4) (b) (4). In general, FDA sets each acceptance range based on the Mean ± 10% of the pivotal clinical trial batch(es) at the time of lot release, i.e., with an acceptance range of no more than 20% at each IVR specification time point. Thus, your counter-proposed acceptance range for the middle specification time point (6 hours) of (b) (4)% for both cytarabine and daunorubicin is not acceptable. Additionally, your proposal to wait for the results of the additional stability testing (data to become completely available July 17) in order to decide on whether you agree or not with FDA's recommended tolerance limit for the last IVR sampling time point (NLT (b) (4)% at (b) (4) hours) is not acceptable because this would not allow FDA to meet the target review time lines. Note also that FDA does not adjust the recommended in vitro drug release and dissolution acceptance criteria to accommodate the proposed shelf-life of a drug product, but rather uses the IVR data of the target drug product batch to evaluate the acceptability of the proposed expiration dating period. We suggest performing simulations to predict the IVR data at the (b) (4) hour time point based on available (b) (4) hour profile data. A Post-Marketing Commitment may also be considered.

Sponsor Response

As discussed with the Agency at the June 22, 2017 CMC teleconference, the Sponsor agrees with the Agency's proposed acceptance criteria for the 1 hour In Vitro Release (IVR) time point and agreed to evaluate the IVR acceptance criteria proposed by the Agency for the 6 hour and (b) (4) hour IVR time points. Please find below the Sponsor's proposal for the 6 hour and final IVR time point.

6 Hour Release - Acceptance Criteria

Table 1 below provides the release data at the 6 hour IVR time point from 8 commercial-scale batches manufactured by (b) (4) Based on these data, the Sponsor proposes to set the acceptance criteria using the same range width (b) (4)%) as that proposed by the Agency ((b) (4)%). However it is proposed (b) (4) (see Table 1 below).

Therefore the proposed 6-hour release acceptance criteria for both cytarabine and daunorubicin is (b) (4)%

Table 1: Commercial – Scale IVR Release Data at 6 Hours

Batch	Cytarabine	Daunorubicin	
			(b) (4)

Final Release Time Point - Acceptance Criteria

The Sponsor has plotted the IVR release profiles for the (b) (4) commercial-scale batches manufactured at (b) (4) Please see Figure 1 and Figure 2 below for the scatter plots with the average % release for both cytarabine and daunorubicin. As can be observed, the data from historical representative batches predict that release criteria proposed by the Agency (NLT (b) (4) %) cannot be reliably achieved at the (b) (4) hour time point.

The Sponsor proposes to have the final IVR release time point at 72 hours as opposed to (b) (4) hours. The rationale for the 72 hour IVR time point is (b) (4)

Therefore, the Sponsor proposes to use the **72 hours** as the final IVR time point and to have the release acceptance criteria at **NLT** (b) (4) **%.**

The Sponsor believes that the proposed IVR acceptance criteria listed below for both Cytarabine and Daunorubicin is appropriate and are discriminatory to previous failed batches (2J004, 3A005 and 3I006) in addition to the formulation variants ([redacted], PF317CD2, PF309CD, PF311CD, PF397D) discussed in the IVR method development report.

IVR Release and Shelf Life Acceptance Criteria

1 hour: **NMT [redacted]%**
6 hours: **[redacted]%**
72 hours: **NLT [redacted]%**

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Agency Comment

To facilitate our review of the counter-proposed IVR acceptance range (b) (4)%) at 6 hours, and the final specification time point (72 hours) provide additional justification in terms of ability to reject "failed" commercial scale Batch # 6K001.

Sponsor Response

The Sponsor has reviewed the release data from the failed CPX-351 drug product batch 6K001 and confirms that this batch does not meet the IVR acceptance criteria proposed by the Sponsor. The result for the 6 hour daunorubicin % release is (b) (4)%, which exceeds the IVR 6 hour release acceptance criteria range of (b) (4)%.

The proposed IVR acceptance criteria listed below for both cytarabine and daunorubicin are discriminatory to all previous failed batches (2J004, 3A005, 3I006 and 6K001) in addition to the formulation variants ((b) (4), PF317CD2, PF309CD, PF311CD, PF397D) discussed in the IVR method development report.

IVR Release and Shelf Life Acceptance Criteria

1 hour: **NMT (b) (4)%**
6 hours: **(b) (4)%**
72 hours: **NLT (b) (4)%**

Agency Comment

In deriving the predicted dissolution data at (b) (4) hours, we suggest using a (b) (4) .

Sponsor Response

The Sponsor acknowledges the Agency's recommendation (b) (4) We agree to perform this assessment and will provide a response to the Agency by July 05, 2017.

Nguyen, Wanda

From: Nguyen, Wanda
Sent: Wednesday, July 05, 2017 3:53 PM
To: 'Fojan Zamanian'; Robin Hume
Subject: NDA 209401 Vyxeos--Rationale for Contraindication

Good Afternoon,

Regarding your submission dated March 31, 2017 for NDA 209401 CPX-351, we have the following information requests. Please respond via email by **12 PM (ET) on July 6, 2017**.

We were inquiring as to what the rationale was to (b) (4) ?

Thanks,
Wanda

Wanda Nguyen, PharmD
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

10903 New Hampshire Avenue |Silver Spring, MD 20993
Wanda.Nguyen@fda.hhs.gov | 301-796-2808

FDA U.S. FOOD & DRUG ADMINISTRATION

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/s/

WANDA D NGUYEN
07/28/2017

MEMORANDUM OF TELECONFERENCE

Teleconference Date: June 29, 2017

Application Number: NDA 209401
Product Name: Cytarabine and Daunorubicin Liposome for Injection
Sponsor/Applicant Name: Celator Pharmaceuticals (a Jazz Pharmaceuticals company)

Subject: Weekly CMC Review Team Status Meeting

FDA Participants
Office of Pharmaceutical Quality:
Sherita McLamore-Hines, CMC Lead, OPQ/ONDP
Christina Cappaci-Daniels, Acting Quality Assessment Lead, OPQ/OPF/DIA
Kumar Janoria, Process Reviewer, OPQ/OPF
David Bateman, Microbiology Reviewer, OPQ/OPF
Charles Jewell, Drug Substance Reviewer, OPQ/ONDP
Gerlie Gieser, Biopharmaceutics Reviewer, OPQ/ONDP
Teshara G. Bouie, Acting Quality Assessment Lead, OPQ/OPRO

Sponsor/Applicant Participants
Jazz Pharmaceuticals:
Robin Hume, Senior Director, Global Regulatory Affairs
Charles LaPree, Vice President, Global Regulatory Affairs
Barry Liboiron, Director, Biophysical Characterization & Advanced Solutions, Translational Research
Les Mintzmyer, Vice President, Manufacturing and Technical Operations
Kieran O'Donoghue, Director, Global Regulatory Affairs, CMC
(b) (4) Consultant
Paul Tardi, Senior Director, Pre-formulation, Translational Research
Sherwin Xie, Senior Director, Analytical R&D, Translational Research
Fojan Zamanian, Director, Global Regulatory Affairs

1.0 BACKGROUND:

Purpose: Update review progress and discuss issues identified during the week.

2.0 DISCUSSION:

Biopharm – the following information request was sent to the applicant on 6/29 prior to the tcon:

1. To facilitate our review of the counter-proposed IVR acceptance range ((b) (4)%) at 6 hours, and the final specification time point (72 hours) provide additional justification in terms of ability to reject "failed" commercial scale Batch # 6K001.

2. In deriving the predicted dissolution data at (b) (4) hours, we suggest using (b) (4) .

The Agency indicated that 6K001 is of particular interest because this Process Validation Batch had IVR profile similarity factors (f_2) for both cytarabine and daunorubicin that were <50 relative to the pivotal Phase 3 clinical trial batches, so the approved IVR acceptance criteria should be able to reject this and similar batches. The Agency also recommended that the Jazz plot the IVR profiles with and without the observed IVR data at (b) (4) and 72 hours so it would be easier to decide which plot-fitting function to use. The Agency inquired whether Jazz would be able to respond to the follow up IR by the middle of next week. Jazz will discuss internally and get back to the Agency with a timeframe for their response.

PAI – In regards to the 483s issued after the PAI inspection at (b) (4) Jazz will work closely with (b) (4) and respond to the 483s within 15 business days.

Process – Additional Process IRs will be issued by the end of next week.

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/s/

TESHARA G BOUIE
06/30/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209401

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Celator Pharmaceuticals, Inc. (a Jazz Pharmaceuticals Company)
3180 Porter Drive
Palto Alto, CA 94304

ATTENTION: Robin L. Hume, MS, RAC
Senior Director, Regulatory Affairs

Dear Ms. Hume:

Please refer to your New Drug Application (NDA) dated and received March 31, 2017, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Cytarabine and Daunorubicin Liposome for Injection, 100 mg and 44 mg per vial.

We also refer to your correspondence, dated and received March 31, 2017, requesting review of your proposed proprietary name, Vyxeos.

We have completed our review of the proposed proprietary name, Vyxeos and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your March 31, 2017, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Neil Vora in the Office of Surveillance and Epidemiology, at (240) 402-4845. For any other information regarding this application, contact Wanda Nguyen, Regulatory Project Manager, in the Office of New Drugs at (301) 796-2808.

Sincerely,

{See appended electronic signature page}

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

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/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
06/21/2017

Nguyen, Wanda

From: Nguyen, Wanda
Sent: Tuesday, June 20, 2017 1:23 PM
To: 'Fojan Zamanian'
Subject: NDA 209401 CPX-351 Information Request

Follow Up Flag: Follow up
Flag Status: Flagged

Good Morning Fojan,

Regarding your submission dated March 31, 2017 for NDA 209401 CPX-351, we have the following information requests. Please respond via email by **12 PM (ET) on June 28, 2017**, followed with a formal submission to the NDA.

We note that in study 301, 96 patients on the Vyxeos arm experienced a TEAE from the nervous system or psychiatric disorders SOC excluding hemorrhages and headaches, as well as other toxicities (e.g. sleep disorders, dysgeusia) that would not be expected to interfere with patient functioning (see list of patients and preferred terms included in this count in the attached files). An analysis of the pooled safety population (any dose of Vyxeos) appears to have the same incidence of these events (63% vs 59% in any control arms). As the narratives submitted do not provide sufficient additional data to allow for the a better characterization of these toxicities, please provide any addition details about the individual cases in the attachment including but not limited to the circumstances of their development, concomitant medications, simultaneously occurring toxicities, treatment if relevant, whether they resolved (as noted in a previous IR, the AEOUT variable in the ADAE dataset does not always appear to accurately represent the outcome of that AE) and duration of the toxicity.

Thank You,
Wanda

Wanda Nguyen, PharmD
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

10903 New Hampshire Avenue |Silver Spring, MD 20993
Wanda.Nguyen@fda.hhs.gov | 301-796-2808

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/s/

WANDA D NGUYEN
06/22/2017

Nguyen, Wanda

From: Nguyen, Wanda
Sent: Tuesday, June 20, 2017 1:27 PM
To: 'Fojan Zamanian'
Subject: NDA 209401 - CPX-351

Follow Up Flag: Follow up
Flag Status: Flagged

Good Morning Fojan,

Regarding your submission dated March 31, 2017 for NDA 209401 CPX-351, we have the following information requests. Please respond via email by **12 PM (ET) on June 26, 2017**, followed with a formal submission to the NDA.

> The text for Section 8 of the draft Prescribing Information should be supported by a review and summary of the available published literature regarding drug use in pregnant and lactating women, which should be submitted in Module 1. Your summary omitted human data for the reference listed drugs cytarabine and daunorubicin. For more information, refer to the *Draft Guidance for Industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Thanks,
Wanda

Wanda Nguyen, PharmD
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

10903 New Hampshire Avenue |Silver Spring, MD 20993
Wanda.Nguyen@fda.hhs.gov | 301-796-2808

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/s/

WANDA D NGUYEN
06/22/2017

Nguyen, Wanda

From: Nguyen, Wanda
Sent: Wednesday, June 14, 2017 10:58 AM
To: 'Fojan Zamanian'
Subject: NDA 209401 CPX-351 --FDA Information Request

Follow Up Flag: Follow up
Flag Status: Flagged

Good Morning Fojan,

Regarding your submission dated March 31, 2017 for NDA 209401 CPX-351, we have the following information requests. Please respond via email by **12 PM (ET) on June 23, 2017**, followed with a formal submission to the NDA.

According to the ADSL dataset, USUBJID (b) (6) received CPX-351 as induction and consolidation, and USUBJID (b) (6) received 7+3 induction and 5+2 consolidation. However, according to the exposure dataset (EX), they both received cytarabine (alternative consolidation). Please resolve these discrepancies and provide the actual treatment sequence for each patient.

Thanks,
Wanda

Wanda Nguyen, PharmD
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

10903 New Hampshire Avenue |Silver Spring, MD 20993
Wanda.Nguyen@fda.hhs.gov | 301-796-2808

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/s/

WANDA D NGUYEN
06/14/2017

Nguyen, Wanda

From: Nguyen, Wanda
Sent: Tuesday, June 13, 2017 6:48 AM
To: 'Fojan Zamanian'
Subject: NDA 209401 CPX 351 -- FDA Information Request

Follow Up Flag: Follow up
Flag Status: Flagged

Good Morning Fojan,

Regarding your submission dated March 31, 2017 for NDA 209401 CPX-351, we have the following information requests. We also refer to your response to the FDA Information request, submitted on May 15, 2017 and June 2, 2017. We note that you state in your response, "If (b) (4) and potential modification to the draft labeling should be considered in order to improve the ability of prescribers to prescribe Vyxeos through better comprehension of labeling information."

Please respond via email by **5PM (ET) on June 19, 2017**, followed with a formal submission to the NDA.

We note that you state in your response, " (b) (4) , and potential modification to the draft labeling should be considered in order to improve the ability of prescribers to prescribe Vyxeos through better comprehension of labeling information."

1. Root cause analysis for all use errors or difficulties encountered in the mass of each agent labeling comprehension study and
2. Your proposed labeling modifications to mitigate the use errors or difficulties observed in the study.

Please notify the Agency as soon as possible if you are unable to meet the requested timeline and provide a date for which we can expect your response.

Thanks,
Wanda

Wanda Nguyen, PharmD
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

10903 New Hampshire Avenue |Silver Spring, MD 20993
Wanda.Nguyen@fda.hhs.gov | 301-796-2808

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/s/

WANDA D NGUYEN
06/13/2017

Nguyen, Wanda

From: Nguyen, Wanda
Sent: Tuesday, June 13, 2017 7:17 AM
To: 'Fojan Zamanian'
Subject: NDA 209401 CPX-351--FDA Information Request
Attachments: hearing impairment in CPX treated patients.xlsx; visual impairment in CPX treated patients vs controls.xlsx

Categories: NDA 209401

Good Morning Fojan,

Regarding your submission dated March 31, 2017 for NDA 209401 CPX-351, we have the following information requests. Please respond via email by **5PM (ET) on June 26, 2017**, followed with a formal submission to the NDA.

We note that in study 301, 16 patients on the Vyxeos arm (10.5%) experienced a TEAE that can be grouped into the term "visual impairment" (see list of patients and preferred terms in attached file), compared to only 7 patients (4.6%) on the control arm. An analysis of the pooled safety population (any dose of Vyxeos vs any control arm) produced a signal as well (8.4% vs 4.9%). As the narratives submitted do not provide sufficient additional data to allow for the a better characterization of these toxicities, please provide any addition details about the individual cases in the attachment including but not limited to the circumstances of their development, concomitant medications, simultaneously occurring toxicities, treatment if relevant, whether they resolved (as noted in a previous IR, the AEOUT variable in the ADAE dataset does not always appear to accurately represent the outcome of that AE) and duration of the toxicity.

We also note that in study 301, 3 patients (2%) in the Vyxeos arm experienced a TEAE that can be grouped into the term "hearing impairment" (see list of patients and PTs in the attached file) compared to no patients in the control arm. In the pooled safety population, only patients who received Vyxeos (n=4) experienced a similar AE whereas no patients in any of the control arms on any of the studies experienced these toxicities. Please submit additional details regarding these 4 patients as well.

Thanks,
Wanda

Wanda Nguyen, PharmD
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

10903 New Hampshire Avenue |Silver Spring, MD 20993
Wanda.Nguyen@fda.hhs.gov | 301-796-2808

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/s/

WANDA D NGUYEN
06/13/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209401

INFORMATION REQUEST

Celator Pharmaceuticals, Inc. (a Jazz Pharmaceuticals company)
Attention: Kieran O'Donoghue
Director, Regulatory Affairs CMC
3180 Porter Drive
Palo Alto, CA 94304

Dear Mr. O'Donoghue:

Please refer to your New Drug Application (NDA) dated March 31, 2017, received March 31, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cytarabine and Daunorubicin Liposome for Injection.

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

DRUG PRODUCT:

1. We acknowledge that in vitro release data is tested as part of your temperature cycling studies submitted in Section 3.2.P.8.1. Provide data for all other drug product attributes tested in the temperature cycling studies.

2. In-use stability studies of the reconstituted drug product and drug product diluted with infusion solutions were conducted under ambient temperature conditions. The labeling indicates (b) (4) . Provide stability data for the reconstituted drug product and diluted drug product at the proposed in-use storage conditions of 2-8 °C. Alternatively, provide an adequate justification that the proposed in-use storage conditions of 2-8 °C do not lead to a change in drug product quality attributes.

We request a response to the Drug Product requests no later than **June 20, 2017**.

LABELING:

1. Provide updated carton/container labeling and PI labeling incorporating the presentation of strength in "mg" instead of (b) (4)" as proposed to the Agency on June 1, 2017 (Serial 0018).

2. The appropriate packaging term for your drug product is "single-dose" vials. In the updated carton/container labeling and PI labeling, update the container description to "single-dose" vials instead of "s (b) (4)." Refer to the Guidance for Industry Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use.

We request a response to the Labeling requests no later than **June 22, 2017.**

If you have any questions, please contact me, at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

Teshara G. Bouie, MSA, RAC, OTR/L
CDR, USPHS, Quality Assessment Lead (Acting)
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Teshara Bouie

Digitally signed by Teshara Bouie
Date: 6/13/2017 12:54:35PM
GUID: 508da7230002a24fd4abdd8018af2a08

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209401

INFORMATION REQUEST

Celator Pharmaceuticals, Inc. (a Jazz Pharmaceuticals company)
Attention: Kieran O'Donoghue
Director, Regulatory Affairs CMC
3180 Porter Drive
Palo Alto, CA 94304

Dear Mr. O'Donoghue:

Please refer to your New Drug Application (NDA) dated March 31, 2017, received March 31, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cytarabine and Daunorubicin Liposome for Injection.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response, no later than **June 15, 2017**, in order to continue our evaluation of your NDA.

MICROBIOLOGY:

1. (b) (4)

2. (b) (4)

3. [redacted]

DRUG PRODUCT:

1. Tighten upper limit for Particle Size D90 so that the proposed drug product specifications may reject non-conforming batches such as the aberrant batch [redacted] manufactured without [redacted].
2. Clarify the shelf life acceptance criteria for [redacted] of daunorubicin and cytarabine. The table provided in Section 3.2.P.5.1 indicates [redacted] acceptance criteria of [redacted]%, and the stability data tables in 3.2.P.8 indicate an acceptance criteria of [redacted]%.
3. Provide detailed methods and study report for the [redacted] studies [redacted]

BIOPHARMACEUTICS:

1. Revise Section 3.2.P.5.2 Analytical Procedures to include a concise summary table for the IVR method parameters including the USP apparatus type/capacity, the mini-paddle speed, the volume and the composition of the IVR medium, the temperature, the volume of the test sample (reconstituted formulation) and the sampling time points for in vitro drug release profiling. For the composition of the IVR medium, specify the % w/v of [redacted] added as internal standard for daunorubicin quantification in the IVR samples.

2. For routine QC of CPX-351 Liposome for Injection at batch release and during stability testing, FDA recommends the IVR acceptance criteria below. Revise the Finished Product QC Specifications and other pertinent NDA documents accordingly.

   <u>For both Cytarabine and Daunorubicin:</u>
   1 hour: NMT [redacted]%
   6 hours: [redacted]0%
   [redacted] hours: NLT [redacted]%

If you have any questions, please contact me, at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

Teshara G. Bouie, MSA, RAC, OTR/L
CDR, USPHS, Quality Assessment Lead (Acting)
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Teshara Bouie

Digitally signed by Teshara Bouie
Date: 6/09/2017 09:19:30AM
GUID: 508da7230002a24fd4abdd8018af2a08

MEMORANDUM OF TELECONFERENCE

Teleconference Date: June 8, 2017

Application Number: NDA 209401
Product Name: Cytarabine and Daunorubicin Liposome for Injection
Sponsor/Applicant Name: Celator Pharmaceuticals (a Jazz Pharmaceuticals company)

Subject: Weekly CMC Review Team Status Meeting

FDA Participants
Office of Pharmaceutical Quality:
Anamitro Banerjee, Acting Branch Chief, OPQ/ONDP
Sherita McLamore-Hines, CMC Lead, OPQ/ONDP
Paresma Patel, Drug Product Reviewer, OPQ/ONDP
Maotang Zhou, Process Reviewer, OPQ/OPF
David Bateman, Microbiology Reviewer, OPQ/OPF
Monica Cooper, Drug Substance Reviewer, OPQ/ONDP
Charles Jewell, Drug Substance Reviewer, OPQ/ONDP
Gerlie Gieser, Biopharmaceutics Reviewer, OPQ/ONDP
Teshara G. Bouie, Acting Quality Assessment Lead, OPQ/OPRO

Sponsor/Applicant Participants
Jazz Pharmaceuticals:
Anne Conneely, Associate Director, Technical Operations
Robin Hume, Senior Director, Global Regulatory Affairs
Charles LaPree, Vice President, Global Regulatory Affairs
Barry Liboiron, Director, Biophysical Characterization & Advanced Solutions, Translational Research
Les Mintzmyer, Vice President, Manufacturing and Technical Operations
Kieran O'Donoghue, Director, Global Regulatory Affairs, CMC
(b) (4) Consultant
Paul Tardi, Senior Director, Pre-formulation, Translational Research
Sherwin Xie, Senior Director, Analytical R&D, Translational Research
Fojan Zamanian, Director, Global Regulatory Affairs

1.0 BACKGROUND:

Purpose: Update review progress and discuss issues identified during the week.

2.0 DISCUSSION:

Drug Substance – Jazz was notified that IRs to DMF (b) (4) and DMF (b) (4) are forthcoming and to follow-up with the Holders regarding the response.

Drug Product

- Drug Product Information Requests are forthcoming. Jazz was advised to update the specification table in section P.5. Jazz asked to update specifications table in P.5. once specifications have been finalized from all disciplines. This proposal is acceptable from the Agency.
- The applicant will be asked to tighten acceptance criteria for particle size D90 to exclude the aberrant batch (b) (4) manufactured withou (b) (4).
- Jazz stated they are working with (b) (4) to provide method validation supplies by the end of June or earlier.
- Based on OTR's report, further IRs regarding method details for (b) (4) studies (b) (4) may be pending.

Process – no pending review issues discussed.

Facilities – no pending review issues discussed.

Microbiology – Microbiology Information Requests are forthcoming.

Biopharm

- Biopharm Information Requests related to the In Vitro Release (IVR) Specification are forthcoming.
- Jazz was reminded to submit the IVR profile data of the batches undergoing long-term stability testing as they become available.

Strength Expression – A tcon with Jazz, OPQ, DHP, and DMEPA is scheduled for June 14, 2017 to discuss the issue of strength expression.

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/s/

TESHARA G BOUIE
06/09/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 072939

MEETING MINUTES

Celator Pharmaceuticals, Inc.
Attention: Lisa DeLuca, PhD
200 Princeton South Corporate Center
Suite 180
Ewing, NJ 08628

Dear Dr. DeLuca:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CPX-351 (cytarabine; daunorubicin) Liposome for Injection.

We also refer to the teleconference between representatives of your firm and the FDA on June 7, 2016. The purpose of the meeting was to discuss the need for a potential design of a Quantitative Pivotal Label Comprehension Study.

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

If you have any questions, call me, Alycia Anderson, Regulatory Project Manager, at (240) 402-4270.

Sincerely,

{See appended electronic signature page}

Donna Przepiorka, MD, PhD
Acting Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	A
Meeting Category:	Guidance
Meeting Date and Time:	June 7, 2016; 9:00 a.m. – 10:00 a.m. (ET)
Meeting Location:	Teleconference
Application Number:	IND 072939
Product Name:	CPX-351 (Cytarabine; Daunorubicin) Liposome Injection
Indication:	CPX-351 is being developed for use in the treatment of patients with acute myeloid leukemia (AML). The proposed indication (b) (4) (b) (4)
Sponsor/Applicant Name:	Celator Pharmaceuticals, Inc.
Meeting Chair:	Donna Przepiorka, MD, PhD
Meeting Recorder:	Alycia Anderson

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products
Donna Przepiorka, MD, PhD, Acting Clinical Team Leader
Alycia Anderson, Regulatory Project Manager

Office of Pharmaceutical Quality (OPQ)/Office of New Drug Products (ONDP)
Anamitro Banerjee, PhD, Branch Chief, Branch II, Division of New Drug Products I (DNDP I)
Sherita McLamore-Hines, PhD, Acting Quality Assessment Lead, Branch II, DNDP I

Office of Surveillance and Epidemiology/Division of Medication Error Prevention and Analysis
Lubna Merchant, PharmD, MS, Deputy Director
Yelena Maslov, PharmD, Team Leader
Hina Mehta, Acting Team Leader
Nicole Garrison, PharmD, Reviewer

SPONSOR ATTENDEES

Lisa DeLuca, PhD, Vice President Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209401

INFORMATION REQUEST
PATENT CERTIFICATION OR VERIFICATION

Celator Pharmaceuticals, Inc. (a Jazz Pharmaceuticals Company)
Attention: Robin L. Hume, MS, RAC
Senior Director, Regulatory Affairs
3180 Porter Drive
Palo Alto, CA 94304

Dear Ms. Hume:

Please refer to your New Drug Application (NDA) dated March 31, 2017, received March 31, 2017, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Vyxeos (cytarabine and daunorubicin) liposome for injection.

We also refer to your amendments dated April 26; May 2, 4, 9, 10 (2), 15, 16, 19, 23, 24, 26 (2), and 30; and June 2 (2), 2017. These amendments do not comply with 21 CFR 314.60(f), which was added by the final rule on Abbreviated New Drug Applications and 505(b)(2) Applications; Final Rule, 81 FR 69580 (October 6, 2016). The final rule became effective on December 5, 2016.

Section 314.60(f) requires that an amendment to an unapproved 505(b)(2) application contain an appropriate patent certification or statement described in 21 CFR 314.50(i), or a "recertification" for a previously submitted paragraph IV certification, if approval is sought for changes described in any of the following types of amendments:

- To add a new indication or other condition of use;
- To add a new strength;
- To make other than minor changes in product formulation; or
- To change the physical form or crystalline structure of the active ingredient.

If an amendment to the 505(b)(2) application does not contain a patent certification (or recertification) or statement, the applicant must verify that the proposed change described in the amendment is not one of the types of amendments described above.

We recommend that the cover letter for your response to this information request and for future amendments to your unapproved 505(b)(2) application either:

1) states that the amendment contains a patent certification (or recertification) or statement required by 21 CFR 314.60(f)(1); or

---

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/s/

WANDA D NGUYEN
06/06/2017

Nguyen, Wanda

From: Nguyen, Wanda
Sent: Monday, June 05, 2017 2:12 PM
To: 'Fojan Zamanian'
Subject: NDA209401 CPX-351--FDA Information Request

Good Afternoon Ms. Zamanian,

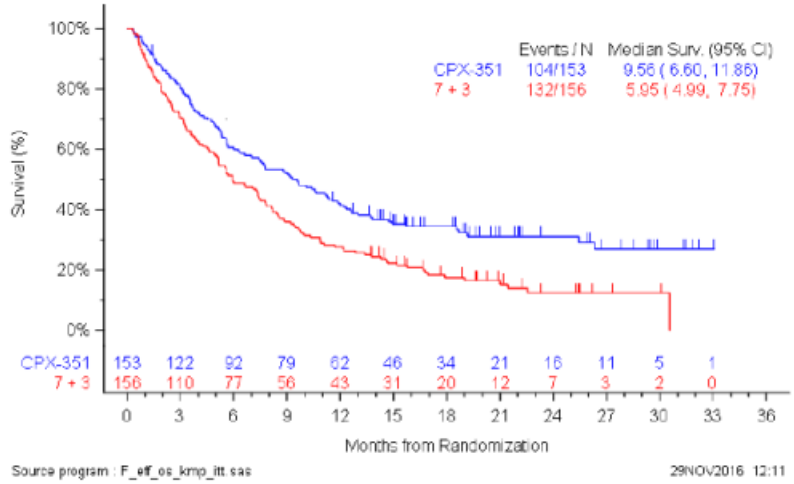
Regarding your submission dated March 31, 2017 for NDA 209401 CPX-351, we have the following information requests.
Please respond via email to by **5PM (ET) on Thursday, June 8, 2017**, followed with a formal submission to the NDA.

Information requests:

Reference is made to the 2.7.3 summary of clinical efficacy Figure 1 and the exposure-response analyses report Figure 3. It seems that you used different cut-off times for the overall survival in these figures.

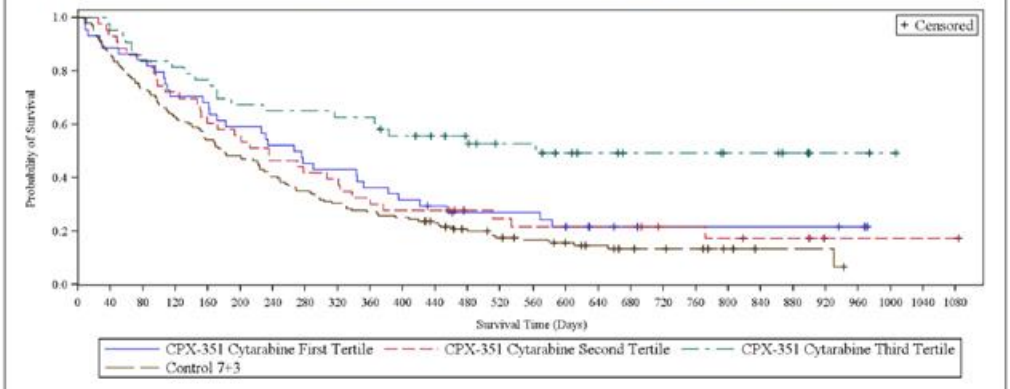
1. Provide your rationale of using different cut-off times.
2. Provide analysis results for the ER (Plasma Exposure) Efficacy Population using the same cut-off time as that for the ITT population (Figure 1).

Figure 1 **Study 301: Kaplan-Meier Curve for Overall Survival, ITT Population**



Source: Study 301 CSR Figure 14.2.1.2.1

Figure 3 Kaplan-Meier Analysis of Overall Survival – ER (Plasma Exposure) Efficacy Population (Cytarabine Tertiles)



	First Tertile (n=44)	Second Tertile (n=43)	Third Tertile (n=43)	7+3 (n=151)
Median Survival Time (Days) (95% CI)	272 (162, 383)	236 (151, 323)	564 (228, -)	181 (148, 236)
p-value (log-rank)	0.0353	0.0667	0.0002	--

Source: EOT Table 1.5.1 and EOT Figure 1.5.1

Please confirm receipt of this notification.

Thanks,
Wanda

Wanda Nguyen, PharmD
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

10903 New Hampshire Avenue |Silver Spring, MD 20993
Wanda.Nguyen@fda.hhs.gov | 301-796-2808

U.S. FOOD & DRUG ADMINISTRATION

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/s/

WANDA D NGUYEN
06/05/2017

Bouie, Teshara

From:	Bouie, Teshara
Sent:	Thursday, June 01, 2017 12:07 PM
To:	Kieran O'Donoghue (Kieran.ODonoghue@jazzpharma.com)
Cc:	Fojan Zamanian (Fojan.Zamanian@jazzpharma.com); Robin Hume (Robin.Hume@jazzpharma.com); Nguyen, Wanda
Subject:	NDA 209401 IR

Hi Kieran,

We acknowledge your response (dated May 19, 2017) to Information Request 8(a) regarding including an in-process control for (b) (4) Based on the data provided we recommend you to tighten your (b) (4) action limit to (b) (4) from the proposed limit of (b) (4)

We request a response by COB June 7, 2017.

Please confirm receipt of this email.

Thanks,

Teshara G. Bouie, MSA, RAC, OTR/L
CDR, United States Public Health Service
Quality Assessment Lead (Acting)
FDA/CDER/OPQ/OPRO
Phone (301) 796-1649
Fax (301) 796-9749

FDA U.S. FOOD & DRUG ADMINISTRATION

Nguyen, Wanda

From: Nguyen, Wanda
Sent: Thursday, June 01, 2017 10:16 AM
To: 'Fojan Zamanian'
Subject: NDA 209401 CPX-351--FDA Information Request

Follow Up Flag: Follow up
Flag Status: Flagged

Good Morning Ms. Zamanian,

Regarding your submission dated March 31, 2017 for NDA 209401 CPX-351, we have the following information requests.
Please respond via email to Comments #1 and #2 by **5PM (ET) on Monday, June 5, 2017**, followed with a formal submission to the NDA.
Please provide a response to Comments #3 and #4 by **5PM (ET) on Thursday, June 8, 2017**, followed with a formal submission to the NDA.

Information Requests:

1. Please clarify the date of data cut off for the Study 301, and explain why the reported data cut off (December 2015) was earlier than the overall survival event date for some patients in the Study 301 data file adtte.

2. Please clarify how you defined the date of induction treatment failure (ITF) when determining the EFS.

3. We seek to determine the robustness of EFS in Study 301. The preferred definition of induction treatment failure (ITF) is no CR within the period of induction (example: within 42 days from the start of the last cycle of induction chemotherapy), and the preferred event date for ITF is study day
   1. Please re-derive the EFS endpoint based on the following definitions, repeat the EFS analysis for each definition, and submit the results to FDA for review.

      a. Method 1: Define ITF as no CR in induction and use study day 1 as the date of ITF, then define the EFS as the time from study randomization to the date of ITF, relapse from CR, or death from any cause, whichever comes first.

      b. Method 2: Define ITF as no CR or CRi in induction and use study day 1 as the date of ITF, then define the EFS as the time from study randomization to the date of ITF, relapse from CR or CRi, or death from any cause, whichever comes first.

      c. Method 3: Define ITF as no CR in induction and use the date of death as the date of ITF, then define the EFS as the time from study randomization to the date of ITF, relapse from CR, or death from any cause, whichever comes first. (Note: This method uses date of death as the event date for ITF. Earlier dates with marrow examinations showing no CR are not used to set the event date for ITF. Patients with induction treatment failure still alive at the time of

analysis should be censored at the date of last assessment just as for patients who are surviving in CR.)

d. Method 4: Define ITF as no CR or CRi in induction and use the date of death as the date of ITF, then define the EFS as the time from study randomization to the date of ITF, relapse from CR or CRi, or death from any cause, whichever comes first. (Note: This method uses date of death as the event date for ITF. Earlier dates with marrow examinations showing no CR or CRi are not used to set the event date for ITF. Patients with induction treatment failure still alive at the time of analysis should be censored at the date of last assessment just as for patients who are surviving in CR or CRi.)

Please then repeat the EFS analyses for Methods 1-4 also censoring at the date of HSCT.

Submit an xpt time-to-event data file with the data and censor variables used for these analyses.

4. Please summarize for Study 301 the number of patients by treatment arm who took other anti-cancer therapies after receiving study therapy. Please submit an xpt data file for the ITT population including the following variables:

   a. Unique subject identifier
   b. Indicator variable for whether the patient took other anti-cancer therapies after receiving study therapy.
   c. Identity of the anti-cancer therapy (for a combination therapy, it is preferred to use the regimen name or acronym rather than listing the start of each drug of the combination separately)
   d. The date of initiation of such anti-cancer therapies.
   e. An Indicator variable for whether the other anti-cancer therapy was HSCT or not.
   f. Whether HSCT was in CR1/CRi1.
   g. The reason to initiate other anti-cancer therapy such as whether it was due to failure of treatment or reaching CR/CRi.

Thanks,
Wanda

Wanda Nguyen, PharmD
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

10903 New Hampshire Avenue |Silver Spring, MD 20993
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/s/

WANDA D NGUYEN
06/05/2017

MEMORANDUM OF TELECONFERENCE

Teleconference Date: May 31, 2017

Application Number: NDA 209401
Product Name: Cytarabine and Daunorubicin Liposome for Injection
Sponsor/Applicant Name: Celator Pharmaceuticals (a Jazz Pharmaceuticals company)

Subject: Weekly CMC Review Team Status Meeting

FDA Participants
Office of Pharmaceutical Quality:
Anamitro Banerjee, Acting Branch Chief, OPQ/ONDP
Gerlie Gieser, Biopharmaceutics Reviewer, OPQ/ONDP
Kumar Janoria, Process Reviewer, OPQ/OPF
Yana Mille, Senior Science Policy Advisor, OPQ/OPPQ
Jibril Abdus-Samad, Pharmacist, OPQ/OPPQ
Jacquin L. Jones, Policy Lead, OPQ/OPPQ
Teshara G. Bouie, Acting Quality Assessment Lead, OPQ/OPRO

Sponsor/Applicant Participants
Jazz Pharmaceuticals:
Jackie Gibbons, Executive Director, Clinical Pharmacology and Early Development
Robin Hume, Senior Director, Global Regulatory Affairs
Charles LaPree, Vice President, Global Regulatory Affairs
Finbar Larkin, Vice President, Technical Operations
Barry Liboiron, Director, Biophysical Characterization & Advanced Solutions, Translational Research
Lawrence Mayer, Senior Vice President, Translational Research
Les Mintzmyer, Vice President, Manufacturing and Technical Operations
Kieran O'Donoghue, Director, Global Regulatory Affairs, CMC
(b) (4) Consultant
Paul Tardi, Senior Director, Pre-formulation, Translational Research
Sherwin Xie, Senior Director, Analytical R&D, Translational Research
Fojan Zamanian, Director, Global Regulatory Affairs

(b) (4)

1.0 BACKGROUND:

Purpose: Update review progress and discuss issues identified during the week.

2.0 DISCUSSION:

Drug Substance – no pending review issues discussed.

Drug Product – Jazz stated they are on track to submit the pending IR requests

Process- The Agency requests [redacted] specifications to be tightened to ≤ [redacted] from ≤ [redacted]. Additional Process IR forthcoming.

Facilities – no pending review issues discussed.

Microbiology – no pending review issues discussed.

Biopharm – The Agency requested Jazz to provide a short interpretation of the bone marrow PK results. Jazz explained the inherent technical limitations of tissue concentration measurements, and indicated that the drugs in CPX-351 are "completely bioavailable". Jazz will provide a summary of cumulative excretion data.

Strength Expression – Jazz stated they are on track to submit the Labeling Comprehensive Study by June 5, 2017. The Agency will schedule a tcon with Jazz, OPQ, DHP, and DMEPA to discuss only the issue of strength expression the week of June 14, 2017.

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/s/

TESHARA G BOUIE
06/01/2017

Nguyen, Wanda

From: Nguyen, Wanda
Sent: Tuesday, May 30, 2017 7:43 AM
To: 'Fojan Zamanian'
Subject: NDA 209401 CPX-351--FDA Information Request

Good Morning Ms. Zamanian,

Regarding your submission dated March 31, 2017 for NDA 209401 CPX-351, we have the following information requests.

Please respond via email by **5PM (ET) on June 7, 2017,** followed with a formal submission to the NDA.

1) There are 60 patients from study 301 (see attached dataset) for whom the ADAE dataset includes grade 5 AEs, yet under the variable for AEOUT, they are listed as "Recovered/resolved," with a few listed as "recovered/resolved with sequelae." In the ISS dataset, this was the case for patients in study 206 as well. Since these were grade 5 AEs that were ongoing at the time of death, please clarify why these terms were used, and submit a revised dataset that uses accurate terms for the AOUT variable.
2) For study 301 and the ISS, please clarify which dataset, if any, contains the investigator reported (verbatim) terms for treatment discontinuation that includes any comments in the eCRFs (in addition to the category picked from the drop down list provided to them).
3) We have noted multiple inconsistencies between the ADSL, ADLB and ADAE datasets and/or eCRFs as well as the patient narratives with regard to reasons provided for treatment discontinuation for various subjects. Please provide justification for the terms used for the following subjects:
    a. USUBJID (b) (6) - disposition term in the ADSL dataset was progressive disease/lack of response, but the patient had a BM that showed 70% cellularity and no blasts, with persistent grade 4 neutropenia and thrombocytopenia, such that it appears the reason for discontinuation was actually toxicity rather than lack of efficacy.
    b. USUBJID (b) (6) disposition term is "patient will receive a stem cell transplant" but the patient received another therapy 40 days later and "Transplant date" is missing.
4) USUBJID (b) (6) is considered to have a best response of CR, but it is noted that per the ADLB dataset, there is no BM reported until after consolidation. Since per the protocol, only patients with CR/CRi after 1-2 induction cycles were eligible for consolidation, the missing data for this subject during/post-induction should be coded as "non-responder" for the CR/CRi endpoint; please justify including this patient as a complete responder.
5) For USUBJID (b) (6) : disposition term is "patient will receive a stem cell transplant," although it appears that the patient relapsed soon after having treatment discontinued and proceeded to salvage instead of HSCT; indeed, the transplant date is missing. However, the narrative states that "On day 39, the subject was taken off study and received Fludarabine and Busulfana dn an allogeneic transplant." These medications are not included in the CM or ADCM datasets, and as noted earlier, there is no transplant date in the ADSL dataset. Please clarify this discrepancy.
6) USUBJID (b) (6) has a treatment start date of (b) (6) according to the ADSL dataset. However, according to the ADLB dataset, the patient had a BM aspirate and biopsy which revealed 22-25% blasts on (b) (6), and then another one on (b) (6) which showed 20% blasts. That dataset also contains labs that were done on (b) (6), which are labeled as "induction day 7." Finally, the induction

1 day 1 date in this dataset is (b) (6). The patient doesn't have an IEVFL of yes which might indicate that he received prior treatment for AML rather than only an HMA for MDS which would have been allowed for by the protocol. Please submit any necessary data to resolve these inconsistencies.

Thanks,
Wanda

Wanda Nguyen, PharmD
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

10903 New Hampshire Avenue |Silver Spring, MD 20993
Wanda.Nguyen@fda.hhs.gov | 301-796-2808

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/s/

WANDA D NGUYEN
05/31/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209401

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

Celator Pharmaceuticals, Inc. (a Jazz Pharmaceuticals Company)
Attention: Robin L. Humes, MS, RAC
Senior Director, Regulatory Strategy
3180 Porter Drive
Palo Alto, CA 94304

Dear Ms. Humes:

Please refer to your New Drug Application (NDA) dated March 31, 2017, received March 31, 2017, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Vyxeos (cytarabine and daunorubicin) liposome for injection.

We also refer to your amendments dated September 30, 2016; April 26, 2017; and May 2 (2), 4, 9, 10 (2), 15, 16, 19, 23, 24, and 26 (2), 2017.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is September 30, 2017**.**

However, we plan to act early on this application under an expedited review, provided that no significant application deficiencies or unexpected shifts in work priorities or team staffing prevent an early action.

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

September 7, 2017. This date conforms to the 21st Century Review timeline for your application. If our review continues on an expedited timeline, we may communicate revised dates for labeling and postmarketing requirement/commitment requests.

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

Chemistry, Manufacturing, and Controls

The strength must be based on each active ingredient in the combination product and should be expressed in mg per vial for each ingredient. The Agency does not agree with the use of the terms (b) (4) or (b) (4) in reference to the dosing strength of Vyxeos (cytarabine and daunorubicin) liposome for injection.

If your 505(b)(2) application relies on FDA's finding of safety and/or effectiveness for a listed drug, we recommend that the cover letter for amendments to your unapproved 505(b)(2) application either: 1) state that the amendment contains a patent certification (or recertification) or statement required by 21 CFR 314.60(f)(1); or 2) verify that the proposed change described in the amendment is not one of the types of amendments described in 21 CFR 314.60(f)(1), as appropriate.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances, and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

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

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

If you have any questions, call Wanda Nguyen, Regulatory Project Manager, at (301) 796-2808.

Sincerely,

{See appended electronic signature page}

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

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/s/

THERESA A CARIOTI
05/30/2017
Signing on behalf of Dr. Ann Farrell

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209401

INFORMATION REQUEST

Celator Pharmaceuticals, Inc. (a Jazz Pharmaceuticals company)
Attention: Kieran O'Donoghue
Director, Regulatory Affairs CMC
3180 Porter Drive
Palo Alto, CA 94304

Dear Mr. O'Donoghue:

Please refer to your New Drug Application (NDA) dated March 31, 2017, received March 31, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cytarabine and Daunorubicin Liposome for Injection.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response, no later than **June 2, 2017**, in order to continue our evaluation of your NDA.

MICROBIOLOGY:

1. We acknowledge the (b) (4) e validation studies, however additional information is required to assess these validation studies. (b) (4)

Comment:

(b) (4)

[redacted] Therefore, please use [redacted] for future sterilization validation studies.

DRUG PRODUCT:

2. Provide tightened shelf life acceptance criteria for [redacted] described in the pharmaceutical development report and batch analysis provided in the NDA submission.

3. Provide raw data for particle size distribution and include [redacted] measurements for commercial batches.

4. Provide evidence for the proposed [redacted] You may also provide any available data from studies to characterize [redacted].

If you have any questions, please contact me, at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

Teshara G. Bouie, MSA, RAC, OTR/L
CDR, USPHS, Quality Assessment Lead (Acting)
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Teshara Bouie

Digitally signed by Teshara Bouie
Date: 5/26/2017 12:47:02PM
GUID: 508da7230002a24fd4abdd8018af2a08

MEMORANDUM OF TELECONFERENCE

Teleconference Date: May 25, 2017

Application Number: NDA 209401
Product Name: Cytarabine and Daunorubicin Liposome for Injection
Sponsor/Applicant Name: Celator Pharmaceuticals (a Jazz Pharmaceuticals company)

Subject: Weekly CMC Review Team Status Meeting

FDA Participants
Office of Pharmaceutical Quality:
Anamitro Banerjee, Acting Branch Chief, OPQ/ONDP
Charles Jewell, Drug Substance Reviewer, OPQ/ONDP
Sherita McLamore-Hines, CMC Lead, OPQ/ONDP
Paresma Patel, Drug Product Reviewer, OPQ/ONDP
Gerlie Gieser, Biopharmaceutics Reviewer, OPQ/ONDP
Maotang Zhou, Process Reviewer, OPQ/OPF
David Bateman, Microbiology Reviewer, OPQ/OPF
Teshara G. Bouie, Acting Quality Assessment Lead, OPQ/OPRO

Sponsor/Applicant Participants
Anne Conneely, Associate Director, Technical Operations
Jackie Gibbons, Executive Director, Clinical Pharmacology and Early Development
Robin Hume, Senior Director, Global Regulatory Strategy
Charles LaPree, Vice President, Global Regulatory Affairs
Barry Liboiron, Director, Biophysical Characterization & Advanced Solutions, Translational Research
Les Mintzmyer, Vice President, Manufacturing and Technical Operations
Kieran O'Donoghue, Director, Global Regulatory Affairs, CMC
(b) (4) Consultant
Paul Tardi, Senior Director, Preformulation, Translational Research
Sherwin Xie, Senior Director, Analytical R&D, Translational Research
Fojan Zamanian, Director, Global Regulatory Strategy

1.0 BACKGROUND:

Purpose: Update review progress and discuss issues identified during the week.

2.0 DISCUSSION:

- Assay for drug substance and lipids should be (b) (4) based on batch history and target drug substance to lipid ratio.

- The Agency questioned if the applicant had performed any additional studies to characterize the liposomes as [redacted] (b) (4) Jazz stated they would check for additional [redacted] (b) (4) images.

- The Agency requested [redacted] (b) (4) data when the applicant submits their particle size distribution data.

- Jazz will respond to the remaining Biopharmaceutics information requests by May 31, 2017. Regarding the request to provide full IVR profile data at the current stability time point, Jazz indicated that the IVR method validation study had determined IVR profiles using the sampling time points of interest to FDA. FDA indicated that the data from such validation study may be acceptable if the batch used is a pivotal clinical trial batch. Otherwise, Jazz will submit (whenever available) the requested IVR profile data (using the sampling points at [redacted] (b) (4) hours) for all batches at the current stability time point.

- Jazz is open to discussing any concerns that FDA might have regarding the bone marrow data during next week's tcon.

- The following Microbiology information request was sent to Jazz May 26, 2017:
    - We acknowledge the [redacted] (b) (4) validation studies, however additional information is required to assess these validation studies. [redacted] (b) (4) .

- Jazz stated they will provide their validation report and proposal regarding the drug product dosing and labeling.

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/s/

TESHARA G BOUIE
05/26/2017

Nguyen, Wanda

From: Nguyen, Wanda
Sent: Wednesday, May 24, 2017 9:27 AM
To: 'Fojan Zamanian'
Subject: NDA 209401 CPX-351--Information Request

Good Morning Ms. Zamanian,

Regarding your submission dated March 31, 2017 for NDA 209401 CPX-351, we have the following information requests.
Additional information is necessary to proceed with our review.

Please respond via email by **5PM (ET) on May 26, 2017,** followed with a formal submission to the NDA.

Information Request:

Reference is made to the exposure-response analyses report, FDA information request dated on May 4, 2017 and your response to FDA information request dated on May 8, 2017. FDA received the programs generating tables in your exposure-response analysis report but not the figures.

Provide all the following information on the exposure-response analyses report: analysis datasets and SAS source codes for all final models (including Kaplan-Meier analysis results in the figures). Please refer to the following link for more details on general expectations of pharmacometric data and models:
https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm

Thanks,
Wanda

Wanda Nguyen, PharmD
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

10903 New Hampshire Avenue |Silver Spring, MD 20993
Wanda.Nguyen@fda.hhs.gov | 301-796-2808

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/s/

WANDA D NGUYEN
05/24/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209401

INFORMATION REQUEST

Celator Pharmaceuticals, Inc. (a Jazz Pharmaceuticals company)
Attention: Kieran O'Donoghue
Director, Regulatory Affairs CMC
3180 Porter Drive
Palo Alto, CA 94304

Dear Mr. O'Donoghue:

Please refer to your New Drug Application (NDA) dated March 31, 2017, received March 31, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cytarabine and Daunorubicin Liposome for Injection.

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

Regarding your May 19, 2017 responses to the Biopharmaceutics Questions in the CMC Information Requests dated May 4, 2017, we have the following comments.

1. The analysis datasets submitted for *in vitro* drug release ((b) (4) When you submit the updated versions of these .xpt datasets including the missing data for the variant batches, provide a means for us to easily identify the batch that was used as reference/target drug product, as well as the Figure or Table number in the 16ARD001 Report that each batch represents (if applicable). Add a data column to allow us to determine whether the time point under the "COND" column corresponds to long-term, accelerated, etc. storage.
2. Additionally, the PSD analysis dataset "SIZE" should include a column for the mean particle size.
3. We acknowledge that you are in the process of converting the requested IVR data into .xpt format. However, it appears that the raw data provided in .xls format do not directly address the question. Specifically, the drug release data for some of the requested

intermediate sampling time points at the current stability time point were not provided, and drug release data for PPQ Batch #4 were not included.

4. For Table 1 of your response, provide for each sampling time point, the cumulative total (encapsulated plus free) amounts of cytarabine and daunorubicin quantified in the bone marrow, expressed as the % of the administered dose.

We request a response to these requests no later than **May 30, 2017**.

If you have any questions, please contact me, at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

Teshara G. Bouie, MSA, RAC, OTR/L
CDR, USPHS, Quality Assessment Lead (Acting)
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Teshara Bouie

Digitally signed by Teshara Bouie
Date: 5/23/2017 11:35:47AM
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209401

INFORMATION REQUEST

Celator Pharmaceuticals, Inc. (a Jazz Pharmaceuticals company)
Attention: Kieran O'Donoghue
Director, Regulatory Affairs CMC
3180 Porter Drive
Palo Alto, CA 94304

Dear Mr. O'Donoghue:

Please refer to your New Drug Application (NDA) dated March 31, 2017, received March 31, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cytarabine and Daunorubicin Liposome for Injection.

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

DRUG PRODUCT

1. Clarify the nominal content of triethanolamine in your drug product. Module 2.3.P.1 has the nominal content listed at (b) (4) mg, and Module 3.2.P.1-Table 1 lists the nominal content as 4 mg. Update the tables and carton/container labels accordingly.
2. The acceptance criteria for osmolality in the drug product release specifications have not been adequately justified. Tighten the acceptance criteria for osmolality at release based on the batch analysis data for commercial scale batches.
3. You have provided elemental impurities assessment in your NDA submission; however, the data for heavy metals in drug product vials is not included in the submission. Provide heavy metals testing data for finished drug product vials.
4. Provide particle size distribution analytical methods for Celator method QC.SOP.037 or (b) (4) Test Method QKTM 24891e/01 that is referenced in the provided transfer validation report QK VB 25185e/01.

PROCESS

1. (b) (4)

(b) (4)

2.

3.

4.

5.

6. Provide English translations for following two documents in the regional information section (3.2.R.1), 5I008 Executed Function Tests and 5I008 Fill weights.

We request a response to these requests no later than **May 24, 2017**.

If you have any questions, please contact me, at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

Teshara G. Bouie, MSA, RAC, OTR/L
CDR, USPHS, Quality Assessment Lead (Acting)
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Teshara Bouie

Digitally signed by Teshara Bouie
Date: 5/18/2017 12:24:23PM
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MEMORANDUM OF TELECONFERENCE

Teleconference Date: May 17, 2017

Application Number: NDA 209401
Product Name: Cytarabine and Daunorubicin Liposome for Injection
Sponsor/Applicant Name: Celator Pharmaceuticals (a Jazz Pharmaceuticals company)

Subject: Weekly CMC Review Team Status Meeting

FDA Participants
Office of Pharmaceutical Quality:
Anamitro Banerjee, Acting Branch Chief, OPQ/ONDP
Benjamin Stevens, Acting Branch Chief, OPQ/ONDP
Sherita McLamore-Hines, CMC Lead, OPQ/ONDP
Katherine Windsor, Drug Substance Reviewer, OPQ/ONDP
Paresma Patel, Drug Product Reviewer, OPQ/ONDP
Kumar Janoria, Process Reviewer, OPQ/OPF
David Bateman, Microbiology Reviewer, OPQ/OPF
Derek Smith, Acting Branch Chief, OPQ/OPF
Christina Capacci-Daniel, Acting Quality Assessment Lead, OPQ/OPF
Richard Lostritto, Acting Associate Director for Science, OPQ/OPPQ
Yana Mille, Senior Science Policy Advisor, OPQ/OPPQ
Jibril Abdus-Samad, Pharmacist, OPQ/OPPQ
Jacquin L. Jones, Policy Lead, OPQ/OPPQ
Teshara G. Bouie, Acting Quality Assessment Lead, OPQ/OPRO

Division of Hematology Products:
Donna Przepiorka, Clinical Team Leader
Aviva Krauss, Clinical Reviewer
Wanda Nguyen, Regulatory Project Manager

Division of Medication Errors and Prevention Analysis:
Mishale Mistry, Acting Associate Director
Hina Mehta, Team Leader
Nicole Garrison, Safety Evaluator

Sponsor/Applicant Participants
Kieran O'Donoghue, Director, Global Regulatory Affairs, CMC
Les Mintzmyer, Vice President, Manufacturing and Technical Operations
Charles LaPree, Vice President, Global Regulatory Affairs (Tentative)
Joanne Curley Executive Director, Global Promotional Regulatory Affairs & Labeling, Regulatory Affairs (G&A)
Robin Hume, Senior Director, Global Regulatory Strategy
Fojan Zamanian, Director, Global Regulatory Strategy

Allen Yang, Vice President, Clinical Development
Arthur Louie, Vice President, Clinical Development
Jackie Gibbons, Executive Director, Clinical Pharmacology and Early Development
Andreas Linkwitz, Senior Director, Project Management

1.0 BACKGROUND:

Purpose: Update review progress and discuss issues identified during the week.

2.0 DISCUSSION:

1. Status of pending Information Requests:
    - Jazz plans to respond to all CMC Information Requests by May 18, 2017.
2. Drug Substance:
    - An Information Request was sent to the Holder of DMF (b) (4) on May 17, 2017. Jazz will follow-up the holder regarding the Holder's response.
3. Drug Product:
    - Additional IRs will be communicated this week. Update modules 2/3 accordingly.
    - Heavy metal testing on the final drug product is needed. Jazz will check with their manufacturer and get back to the Agency.
    - Tighten acceptance criteria based on osmolality.
    - Validation Report requested.
4. Process:
    - Additional IRs will be communicated this week.
5. Biopharm:
    - Jazz requested clarification on Biopharm IR #4. They would like to know what file format (pdf, excel, etc.) the Agency would like to receive data. (Post-meeting note, Jazz was informed that the preferred file format is .xpt.)
6. Strength expressed in Units:
    - The Agency is opposed to the use of (b) (4) for this product. DMEPA requests the timing of the Label Comp Study results. Both Jazz and the Agency will explore other approved combination drug product labeling to determine how similarly situated products were labeled.

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/s/

TESHARA G BOUIE
05/18/2017

Nguyen, Wanda

From: Nguyen, Wanda
Sent: Wednesday, May 17, 2017 1:25 PM
To: 'Fojan Zamanian'
Subject: NDA 209401 CPX-351--FDA Information Request

Follow Up Flag: Follow up
Flag Status: Flagged

Good Morning Ms. Zamanian,

Regarding your submission dated March 31, 2017 for NDA 209401 CPX-351, we have the following information requests. Additional information is necessary to proceed with our review.

Please respond via email by **5PM (ET) on May 23, 2017,** followed with a formal submission to the NDA.

We refer to the response to the FDA Information request submitted on May 15, 2017. We note in your response that preliminary results to validation study 2, Mass of Each Agent are provided. However, you state the final report for validation study 2 is pending completion. Please provide the timeline for submission of the final report for validation study 2, as the submission of the final report of validation study 2 is necessary to proceed with our review.

Thanks,
Wanda

Wanda Nguyen, PharmD
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

10903 New Hampshire Avenue |Silver Spring, MD 20993
Wanda.Nguyen@fda.hhs.gov | 301-796-2808

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/s/

WANDA D NGUYEN
05/17/2017

Nguyen, Wanda

From: Nguyen, Wanda
Sent: Friday, May 12, 2017 10:06 AM
To: 'Fojan Zamanian'
Subject: NDA 209401 CPX-351--FDA Information Request

Good Morning Mr. Zamanian,

Regarding your submission dated March 31, 2017 for NDA 209401 CPX-351, we have the following information requests. Additional information is necessary to proceed with our review.

Please respond via email by **5PM (ET) on May 29, 2017,** followed with a formal submission to the NDA.

1. In general, we note that the computational algorithms in the define.xml use code and reference internal applicant datasets that were not provided. For example, the reference start date from the demographics domain, the computational method used refers to "pdm" dataset. This dataset which is not provided with the submission includes variables such as rfstdtc_yr, rfstdtc_mo etc. These variables aren't present in any of the provided datasets. Please submit a revised define file that contains interpretable computational algorithms plus any referenced datasets in these algorithms. Please also provide the computational algorithm for the Treatment Emergent Flag (AETRTEM) which is missing from the SUPPAE section of the define.xml.

2. Although the ISS datasets contain unique subject identifiers for each subject for each of the studies included, the datasets provided for Study 204 under module 5.3.5.1 for the individual studies do not. Please submit revised data files for this study that include unique subject IDs for each subject for all of the datasets by May 29, 2017.

Thank You,
Wanda

Wanda Nguyen, PharmD
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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Wanda.Nguyen@fda.hhs.gov | 301-796-2808

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/s/

WANDA D NGUYEN
05/12/2017

Bouie, Teshara

From: Bouie, Teshara
Sent: Thursday, May 11, 2017 4:56 PM
To: Kieran O'Donoghue (Kieran.ODonoghue@jazzpharma.com)
Cc: Fojan Zamanian (Fojan.Zamanian@jazzpharma.com); Robin Hume (Robin.Hume@jazzpharma.com); Laiq, Rabiya; Nguyen, Wanda
Subject: NDA 209401 - Information Request

Hi Kieran,

Provide English translations for all representative CoAs from [redacted] (b) (4)) that are submitted in the Control of Excipient Section 3.2.P.4.4 of your NDA.

We request a response no later than May 18, 2017.

Please confirm receipt of the email.

Thanks,

Teshara G. Bouie, MSA, RAC, OTR/L
CDR, United States Public Health Service
Quality Assessment Lead (Acting)
FDA/CDER/OPQ/OPRO
Phone (301) 796-1649
Fax (301) 796-9749

U.S. FOOD & DRUG ADMINISTRATION

Nguyen, Wanda

From: Nguyen, Wanda
Sent: Wednesday, May 10, 2017 4:00 PM
To: 'Fojan Zamanian'
Cc: Robin Hume
Subject: RE: NDA 209401 CPX-351 -- FDA Information Request

Good Afternoon Fojan,

The clinical reviewers do not use SAS. Please submit revised data files for TTE and RSINFO that include unique subject IDs for each subject by **May 16, 2017** to allow for Agency review of these files.

Thank You,
Wanda

From: Fojan Zamanian [mailto:Fojan.Zamanian@jazzpharma.com]
Sent: Friday, May 05, 2017 5:28 PM
To: Nguyen, Wanda
Cc: Robin Hume; Fojan Zamanian
Subject: RE: NDA 209401 CPX-351 -- FDA Information Request

Dear Wanda,

I am writing to request clarification for the following two question. Please confirm receipt.

FDA Information Request Received on April 28, 2017

Question 6

At the pre-NDA meeting, we requested (response to question 5, FDA point 4) an integrated time-to-event data file for all subjects from studies 101, 204, 205, 206 and 301, with a set of minimum particular variables requested. This was submitted as the Tte data file in module 5.3.5.3, ISE, with an additional Dthroot data file. However, it is noted that patients in the Tte file do not have unique subject identifiers, so these data are uninterpretable (multiple subjects are included under many of the subject IDs, as subjects at different sites have the same subjid, and that is the only subject identifier included in this dataset). The same problem was identified in the RSinfo data file, also requested in our responses to the pre-NDA questions (question 5, FDA point 5). Please submit revised data files that include unique subject IDs for each subject by May 29, 2017.

Applicant request for clarification:

The sponsor submitted non-ADaM datasets to address the agency requests for Question 5 points 4 and 5 in the pre-NDA meeting. The DTHROOT data file is a lookup table for the sponsor determined root cause of death (Pre NDA Meeting Question 5 Point 4). The sponsor acknowledges that there is no unique subject identifier provided in these data files (TTE and RSINFO) and provides the SAS codes below that can be implemented to obtain the unique subject identifier to facilitate the agency's review of these data files. The DTHROOT data file consists of the unique subject identifier named SUBJID.

The Following SAS codes can be implemented to obtain unique subject identifiers in RSINFO:

```
proc sql noprint;
```

The following SAS codes can be implemented to obtain unique subject identifiers in TTE:

FDA Information Request Received on May 1, 2017

Question 2

Although the ISS datasets contain unique subject identifiers for each subject for each of the studies included, the datasets provided for Study 204 under module 5.3.5.1 for the individual studies do not. Please submit revised data files for this study that include unique subject IDs for each subject for all of the datasets.

Please respond via email by 3PM on May 29, 2017, followed with a formal submission to the NDA.

Applicant request for clarification:

The sponsor has submitted non-ADaM legacy datasets for the 204 study as per the data submission plan (Pre-NDA briefing material Appendix F) as part of the NDA. Although the legacy datasets do not have the unique subject identifier variable named USUBJID per CDISC definition, the variable SUBJID found in each dataset can be considered unique within the study. This is the variable which was used as the unique subject identifier at the study level to generate all output for the clinical study report. The integrated safety analyses conducted with 204 data did use the unique subject identifier (USUBJID) in the ISS datasets. The sponsor provides the SAS codes below which can be implemented to obtain unique subject identifier (USUBJID) for each 204 dataset. The code illustrates the derivation for AOUTCOME dataset.

I look forward to hearing from you soon.

Kind regards,

Fojan Zamanian
Director, Regulatory Strategy

650.496.2795 (office)
(b) (6) *(mobile)*
fojan.zamanian@jazzpharma.com

From: Fojan Zamanian
Sent: Wednesday, May 03, 2017 4:32 PM
To: Nguyen, Wanda
Cc: Robin Hume; Fojan Zamanian
Subject: RE: NDA 209401 CPX-351 -- FDA Information Request

Dear Wanda,

I am writing to request clarification for the following

Non-hold Comments received on 28 April 2017:

5. **At the pre-NDA meeting, you inquired (Question 9) as to whether Example 4 in the Integrated Summary of Safety (ISS) guidance was acceptable for this application. We responded "No, you will need to submit a full ISS that included includes detailed analysis of all available safety information." The ISS submitted in module 5.3.5.3 includes 1 page of text and 11,586 pages of tables and figures. We do not view the 1 page of text as fulfilling the requirement for an ISS. Submit an ISS by May 29, 2017.**

Jazz request for clarification:

The Sponsor acknowledges the Agency's comment regarding the Integrated Summary of Safety in the current submission, and reference to the pre-NDA meeting minutes.
As CPX-351 is for use in an orphan indication, we intend to submit the ISS under Example 2 in the Integrated Summary of Safety guidance. As per this guidance, the Sponsor intends to take the detailed integrated safety analysis as reported in Module 2.7.4 and also include it in Module 5.3.5.3. Would this address the Agency's concern?

I look forward to hearing from you soon.

Kind regards,

Fojan Zamanian
Director, Regulatory Strategy

650.496.2795 (office)
(b) (6) *(mobile)*
fojan.zamanian@jazzpharma.com

From: Robin Hume
Sent: Friday, April 28, 2017 3:50 PM
To: Nguyen, Wanda
Cc: Fojan Zamanian; Robin Hume
Subject: RE: NDA 209401 CPX-351 -- FDA Information Request

Dear Wanda,

Thank you for your email, I confirm receipt of the request we will respond within the timeframe requested.

Best,
Robin

Robin L. Hume, M.S. RAC
Senior Director, Regulatory Strategy
Therapeutic Area Lead – Hematology/Oncology

650.496.2901 (office)
(b) (6) *(mobile)*
robin.hume@jazzpharma.com

From: Nguyen, Wanda [mailto:Wanda.Nguyen@fda.hhs.gov]
Sent: Friday, April 28, 2017 11:03 AM
To: Robin Hume
Subject: NDA 209401 CPX-351 -- FDA Information Request

Good Afternoon Ms. Hume,

Regarding your submission dated March 31, 2017 for NDA 209401, we have the following clinical comments. Please respond to the comments with a point by point response.
Please respond via email by **3 PM on May 3, 2017**, followed with a formal submission to the NDA.

Non-hold Comments:

1) The ADSL dataset for Study 301 has 458 patients, although only 309 patients were randomized according to the CSR. While only 309 are flagged "Y" for the ITTFL variable, the remaining 149 patients do not appear to be screen failures, as under the SCRNFAIL variable, only 2 patients have "Y," and both of these patients are also flagged as being part of the ITT population. The IEVFL variable is similarly not helpful, as only 25 patients are labeled "Y," and these are all patients who are part of the ITT population as well. Please clarify the status of the 149 patients included in the ADSL dataset who are not part of the ITT population. Provide a response by May 3, 2017.

2) For Study 301: In the DM domain, it is unclear to what the variable RFENDTC refers. Other variables appear to reflect the randomization date (RFSTDTC), date of first study treatment (RFXSTDTC), date of last study treatment (RFXENDTC), date of end of study participation (RFPENDTC) , and date of death (DTHDTC), and these have correlates in the ADSL file , but RFENDTC has no interpretable computational algorithm (the one provided refers to a variable that was not provided in any of the other datasets, namely, RETPHDTC, and it does not correlate with any variable in the ADSL file). For at least some of the patients, this date is not that same as any of the other dates for the variables above. The same appears to be the case for study 205. Please provide clarification regarding this variable and its derivation for all relevant studies. Provide a response by May 3, 2017.

3) Please identify any differences in efficacy outcomes in the NDA submission that differs from the file submitted for the breakthrough designation request. Provide a response by May 3, 2017.

4) Please identify any differences in the data for Sites 002, 004 and 031 submitted 7/18/2016 to IND 072939 and in the current NDA. Provide a response by May 3, 2017.

Please respond via email by **3 PM on May 29, 2017**, followed with a formal submission to the NDA for the following comments.

Non-hold Comments:

5) At the pre-NDA meeting, you inquired (Question 9) as to whether Example 4 in the Integrated Summary of Safety (ISS) guidance was acceptable for this application. We responded "No, you will need to submit a full ISS that included includes detailed analysis of all available safety information." The ISS submitted in module 5.3.5.3 includes 1 page of text and 11,586 pages of tables and figures. We do not view the 1 page of text as fulfilling the requirement for an ISS. Submit an ISS by May 29, 2017.

6) At the pre-NDA meeting, we requested (response to question 5, FDA point 4) an integrated time-to-event data file for all subjects from studies 101, 204, 205, 206 and 301, with a set of minimum particular variables requested. This was submitted as the Tte data file in module 5.3.5.3, ISE, with an additional Dthroot data file. However, it is noted that patients in the Tte file do not have unique subject identifiers, so these data are uninterpretable (multiple subjects are included under many of the subject IDs, as subjects at different sites have the same subjid, and that is the only subject identifier included in this dataset). The same problem was identified in the RSinfo data file, also requested in our responses to the pre-NDA

questions (question 5, FDA point 5). Please submit revised data files that include unique subject IDs for each subject by May 29, 2017.

Please confirm receipt of this notification.

Thank You,
Wanda

Comments to Sponsor

Wanda Nguyen, PharmD
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

10903 New Hampshire Avenue |Silver Spring, MD 20993
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/s/

WANDA D NGUYEN
05/12/2017

Nguyen, Wanda

From: Nguyen, Wanda
Sent: Monday, May 08, 2017 8:43 AM
To: 'Fojan Zamanian'
Cc: Robin Hume
Subject: RE: NDA 209401 CPX-351 -- FDA Information Request

Good Morning Mr. Zamanian,

No, we do not view the detailed integrated safety analysis as reported in Module 2.7.4 (i.e., the SCS) as fulfilling the requirement for an ISS. The text accompanying the tables, figures and datasets in an ISS should address all of the analyses included in these tables and figures and their conclusions; the SCS does not do this. Please submit text to accompany the submitted tables and figures in module 5.3.5.3 by **May 29th, 2017**. Specifically highlight any analyses that were not included in the SCS in this document.

Thanks,

Wanda

From: Fojan Zamanian [mailto:Fojan.Zamanian@jazzpharma.com]
Sent: Wednesday, May 03, 2017 7:32 PM
To: Nguyen, Wanda
Cc: Robin Hume; Fojan Zamanian
Subject: RE: NDA 209401 CPX-351 -- FDA Information Request

Dear Wanda,

I am writing to request clarification for the following

Non-hold Comments received on 28 April 2017:

5. **At the pre-NDA meeting, you inquired (Question 9) as to whether Example 4 in the Integrated Summary of Safety (ISS) guidance was acceptable for this application. We responded "No, you will need to submit a full ISS that included includes detailed analysis of all available safety information." The ISS submitted in module 5.3.5.3 includes 1 page of text and 11,586 pages of tables and figures. We do not view the 1 page of text as fulfilling the requirement for an ISS. Submit an ISS by May 29, 2017.**

Jazz request for clarification:

The Sponsor acknowledges the Agency's comment regarding the Integrated Summary of Safety in the current submission, and reference to the pre-NDA meeting minutes.
As CPX-351 is for use in an orphan indication, we intend to submit the ISS under Example 2 in the Integrated Summary of Safety guidance. As per this guidance, the Sponsor intends to take the detailed integrated safety analysis as reported in Module 2.7.4 and also include it in Module 5.3.5.3. Would this address the Agency's concern?

I look forward to hearing from you soon.

Kind regards,

Fojan Zamanian
Director, Regulatory Strategy

650.496.2795 (office)
(b) (6) *(mobile)*
fojan.zamanian@jazzpharma.com

From: Robin Hume
Sent: Friday, April 28, 2017 3:50 PM
To: Nguyen, Wanda
Cc: Fojan Zamanian; Robin Hume
Subject: RE: NDA 209401 CPX-351 -- FDA Information Request

Dear Wanda,

Thank you for your email, I confirm receipt of the request we will respond within the timeframe requested.

Best,
Robin

Robin L. Hume, M.S. RAC
Senior Director, Regulatory Strategy
Therapeutic Area Lead – Hematology/Oncology

650.496.2901 (office)
(b) (6) *(mobile)*
robin.hume@jazzpharma.com

From: Nguyen, Wanda [mailto:Wanda.Nguyen@fda.hhs.gov]
Sent: Friday, April 28, 2017 11:03 AM

To: Robin Hume
Subject: NDA 209401 CPX-351 -- FDA Information Request

Good Afternoon Ms. Hume,

Regarding your submission dated March 31, 2017 for NDA 209401, we have the following clinical comments. Please respond to the comments with a point by point response.
Please respond via email by **3 PM on May 3, 2017**, followed with a formal submission to the NDA.

Non-hold Comments:

1) The ADSL dataset for Study 301 has 458 patients, although only 309 patients were randomized according to the CSR. While only 309 are flagged "Y" for the ITTFL variable, the remaining 149 patients do not appear to be screen failures, as under the SCRNFAIL variable, only 2 patients have "Y," and both of these patients are also flagged as being part of the ITT population. The IEVFL variable is similarly not helpful, as only 25 patients are labeled "Y," and these are all patients who are part of the ITT population as well. Please clarify the status of the 149 patients included in the ADSL dataset who are not part of the ITT population. Provide a response by May 3, 2017.

2) For Study 301: In the DM domain, it is unclear to what the variable RFENDTC refers. Other variables appear to reflect the randomization date (RFSTDTC), date of first study treatment (RFXSTDTC), date of last study treatment (RFXENDTC), date of end of study participation (RFPENDTC) , and date of death (DTHDTC), and these have correlates in the ADSL file , but RFENDTC has no interpretable computational algorithm (the one provided refers to a variable that was not provided in any of the other datasets, namely, RETPHDTC, and it does not correlate with any variable in the ADSL file). For at least some of the patients, this date is not that same as any of the other dates for the variables above. The same appears to be the case for study 205. Please provide clarification regarding this variable and its derivation for all relevant studies. Provide a response by May 3, 2017.

3) Please identify any differences in efficacy outcomes in the NDA submission that differs from the file submitted for the breakthrough designation request. Provide a response by May 3, 2017.

4) Please identify any differences in the data for Sites 002, 004 and 031 submitted 7/18/2016 to IND 072939 and in the current NDA. Provide a response by May 3, 2017.

Please respond via email by **3 PM on May 29, 2017**, followed with a formal submission to the NDA for the following comments.

Non-hold Comments:

5) At the pre-NDA meeting, you inquired (Question 9) as to whether Example 4 in the Integrated Summary of Safety (ISS) guidance was acceptable for this application. We responded "No, you will need to submit a full ISS that included includes detailed analysis of all available safety information." The ISS submitted in module 5.3.5.3 includes 1 page of text and 11,586 pages of tables and figures. We do not view the 1 page of text as fulfilling the requirement for an ISS. Submit an ISS by May 29, 2017.

6) At the pre-NDA meeting, we requested (response to question 5, FDA point 4) an integrated time-to-event data file for all subjects from studies 101, 204, 205, 206 and 301, with a set of minimum particular variables requested. This was submitted as the Tte data file in module 5.3.5.3, ISE, with an additional

Dthroot data file. However, it is noted that patients in the Tte file do not have unique subject identifiers, so these data are uninterpretable (multiple subjects are included under many of the subject IDs, as subjects at different sites have the same subjid, and that is the only subject identifier included in this dataset). The same problem was identified in the RSinfo data file, also requested in our responses to the pre-NDA questions (question 5, FDA point 5). Please submit revised data files that include unique subject IDs for each subject by May 29, 2017.

Please confirm receipt of this notification.

Thank You,
Wanda

Comments to Sponsor

Wanda Nguyen, PharmD

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

10903 New Hampshire Avenue |Silver Spring, MD 20993
Wanda.Nguyen@fda.hhs.gov | 301-796-2808

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/s/

WANDA D NGUYEN
05/12/2017

Nguyen, Wanda

From: Nguyen, Wanda
Sent: Thursday, May 04, 2017 9:19 AM
To: 'Fojan Zamanian'
Subject: NDA 209401 CPX-351 --FDA information request

Follow Up Flag: Follow up
Flag Status: Flagged

Categories: NDA 209401

Good Morning Mr. Zamanian,

Regarding your submission dated March 31, 2017 for NDA 209401 CPX-351, we have the following information requests. Additional information is necessary to proceed with our review.
Please respond via email by **5PM (ET) on May 8, 2017,** followed with a formal submission to the NDA.

Information Request:

1. Provide the following information on the population pharmacokinetic analysis: NONMEM model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submitted these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).
2. Provide the following information on the exposure-response analyses for pharmacodynamic markers, efficacy and safety: SAS source codes for all final models. Submitted these files as ASCII text files with *.txt extension (e.g.: myfile_sas.txt).

   Please refer to the following link for more details on general expectations of pharmacometric data and models:
   https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm

Please confirm receipt of notification.

Thanks,

Wanda

Wanda Nguyen, PharmD
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

10903 New Hampshire Avenue |Silver Spring, MD 20993

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/s/

WANDA D NGUYEN
05/12/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209401

INFORMATION REQUEST

Celator Pharmaceuticals, Inc. (a Jazz Pharmaceuticals company)
Attention: Kieran O'Donoghue
Director, Regulatory Affairs CMC
3180 Porter Drive
Palo Alto, CA 94304

Dear Mr. O'Donoghue:

Please refer to your New Drug Application (NDA) dated March 31, 2017, received March 31, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cytarabine and Daunorubicin Liposome for Injection.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a written response by **Thursday, May 18, 2017**.

DRUG PRODUCT and PROCESS

1. Provide the executed batch records for the registration lots (i.e. batches 1C001, 1D001, 1E003) in addition to PPQ #1 (Batch 5I008) provided already.

2. During the application orientation meeting held on 27-Apr-2017, you indicated that process changes have been implemented including (b) (4) .
   - Provide batch release data and all available stability data for process validation batches of drug product manufactured with the proposed commercial process.
   - Provide any corresponding updates to the manufacture process sections of the NDA.
   - Provide the executed batch record for the PPQ #4 batch, as well as the intended master batch records.

3. We acknowledge the letter of authorization for DMF (b) (4) to reference information for the (b) (4) 50 mL glass vials used as part of your container closure system. Provide a

representative certificate of analysis from the manufacturer of the vials. Additionally, provide the exact location in the DMF and submission date for the referenced CMC information for the vials used in your proposed drug product.

4. Provide English translations of the representative CoAs for (b) (4) submitted in section 3.2.P.6.

5. Provide statement of compliance to pertinent 21CFR regulations (b) (4)

6. Provide equipment compatibility data to demonstrate that the drug product impurity profile was not adversely affected upon contacting (b) (4)

7. As per CFR 211.103 and CFR211.186(b)(7) provide consolidated reconciliation tables for all exhibition batches including theoretical yield, target yield specification, and actual yield for each unit operation and total production, wherever is applicable. Provide justification for any significant waste and/or rejections and batch to batch variability. Also, submit above information for the PPQ batches as well.

8. In reference to Section 3.2.P.3.4 of the NDA submission (Table 1) concerning controls of critical steps and intermediates, we have the following recommendations:
   a. (b) (4)
   b.

c. (b) (4)

d.

e.

BIOPHARMACEUTICS

1. Submit an analysis dataset (in .xpt format) containing the cytarabine and the daunorubicin *In Vitro* Release (IVR) profile data of the drug product batches, generated using the proposed commercial QC IVR method (consistent with the summary information provided in Table 1 of 3.2.P.5.4). Include all the batches that were used in the clinical studies, stability testing and (successful/failed) process validation, as well as for IVR method development studies (e.g. for investigation of the method's discriminating power). In addition to data columns indicating the batch use (e.g., Phase 3 clinical/ registration/ process validation/ variant for lipid composition) and the conditions of IVR testing (e.g., long-term stability/Month 12), the dataset should include columns to flag excluded data, and to provide the reason/justification for the exclusion (e.g., equipment failure, OOS). Any IVR data from the frozen/liquid drug product batches should also be flagged.

2. Submit a similar analysis dataset for liposome particle size distribution (including the mean, d_{10}, d_{50}, and d_{90} values).

3. We understand that (b) (4) is used as internal standard for daunorubicin quantification in the IVR test samples. Clarify why (b) (4) is added (directly) to the proposed IVR medium. Provide data regarding the robustness of the IVR method in the presence and absence of (b) (4) in the QC IVR medium.

4. At the current and subsequent stability time points, provide IVR profile data (n=12, mean/%RSD/min/max/individual; at (b) (4) 96 hours) for all the drug product batches undergoing stability testing.

5. In relation to Figures 3A and 3B of Lim *et al* [Leukemia Research 34 (2010), 1214 - 1223], provide a table summarizing the time course profiles of cytarabine and daunorubicin concentrations in bone marrow following the first injection of CPX-351 injection in the animal model. Based on these drug concentration data, provide also the cumulative *in vivo* drug release from CPX-351 at each time point.

MICROBIOLOGY

1. Provide the following information regarding the routine environmental monitoring program:
   a. The alert and action levels for air, surface and personnel monitoring in each of the different room grades.
   b. Actions taken when levels are exceeded.
   c. A description of the methods used to monitor the total aerobic microbial count and the total combined yeast and mold count.
   d. A description of the routine (b) (4) monitoring program, including sites which are monitored and frequency of sampling. Also include (b) (4) alert and action levels for bioburden and actions taken when levels are exceeded.

2. Provide the following information regarding the validation of the (b) (4):
   a. (b) (4)
   b.
   c.
   d.
   e.
   f.
   g.
   h.
   i. The acceptance criteria for production and validation cycles.

3. Provide the following information regarding the validation of the (b) (4) :

a. [redacted]
b.
c.
d.
e.
f.

4. Provide the following information regarding the [redacted] validation for each of the four [redacted]:
   a. [redacted]
   b. The acceptance criteria for production and validation cycles.
   c. [redacted]
   d.
   e.

5. Clarify how [redacted] is utilized.

6. Clarify how [redacted].

7. Provide the following information regarding media fill simulations:
   a. The results for three recent media fill simulations including either the vial size intended for commercial production of the drug product or bracketed results which cover the intended vial size.
   b. A list of interventions simulated during a media fills.
   c. The media used and incubation conditions for media-filled vials.
   d. The results of growth promotion studies and environmental monitoring conducted during the aseptic processing simulation.
   e. The frequency of aseptic processing simulations.
   f. A comparison of the parameters used during a media fill and the parameters used for commercial production.

If you have any questions, please contact me, at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

Teshara G. Bouie, MSA, RAC, OTR/L
CDR, USPHS, Quality Assessment Lead (Acting)
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Luz Rivera

Digitally signed by Luz Rivera
Date: 5/04/2017 12:55:14PM
GUID: 502abbaa000025b89fdb52a977a3d336

Nguyen, Wanda

From: Nguyen, Wanda
Sent: Monday, May 01, 2017 7:51 AM
To: 'Robin Hume'
Subject: NDA 209401 CPX-351- FDA Information Request

Follow Up Flag: Follow up
Flag Status: Flagged

Good Morning Ms. Hume,

Regarding your submission dated March 31, 2017 for NDA 209401 CPX-351, we have the following information requests.
Additional information is necessary to proceed with our review.
Please respond via email by 3PM on **May 15, 2017,** followed with a formal submission to the NDA.

Information Request:

1. A summary of preliminary analyses and evaluations, including formative studies;
    a. Include in your summary a discussion of key findings and any changes made to your product or labeling, including how the findings were used to update the user interface and risk analysis
2. Validation testing details including:
    a. Root cause analysis for all use errors or difficulties for questions 9 through 12 of the questionnaire
3. A summary of any changes made to the user interface (e.g., product design or label and labeling changes) after completion of the label comprehension study, including a description of how the changes do not require further validation through a supplemental label comprehension study.

Please confirm receipt of this notification.

Thank You,
Wanda

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/s/

WANDA D NGUYEN
05/01/2017

Nguyen, Wanda

From: Nguyen, Wanda
Sent: Monday, May 01, 2017 8:06 AM
To: 'Robin Hume'
Subject: NDA 209401 CPX-351-FDA Information Requests

Follow Up Flag: Follow up
Flag Status: Flagged

Good Morning Ms. Hume,

Regarding your submission dated March 31, 2017 for NDA 209401 CPX-351, we have the following information requests.
Additional information is necessary to proceed with our review.

Information Request:

Please respond via email by 3PM on **May 3, 2017,** followed with a formal submission to the NDA.

1. In general, we note that the computational algorithms in the define.xml use code and reference internal applicant datasets that were not provided. For example, the reference start date from the demographics domain, the computational method used refers to "pdm" dataset. This dataset which is not provided with the submission includes variables such as rfstdtc_yr, rfstdtc_mo etc. These variables aren't present in any of the provided datasets. Please submit a revised define file that contains interpretable computational algorithms plus any referenced datasets in these algorithms. Please also provide the computational algorithm for the Treatment Emergent Flag (AETRTEM) which is missing from the SUPPAE section of the define.xml.

Please respond via email by 3PM on **May 29, 2017,** followed with a formal submission to the NDA.

2. Although the ISS datasets contain unique subject identifiers for each subject for each of the studies included, the datasets provided for Study 204 under module 5.3.5.1 for the individual studies do not. Please submit revised data files for this study that include unique subject IDs for each subject for all of the datasets.

Thank You,
Wanda

Wanda Nguyen, PharmD
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

10903 New Hampshire Avenue |Silver Spring, MD 20993
Wanda.Nguyen@fda.hhs.gov | 301-796-2808

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/s/

WANDA D NGUYEN
05/01/2017

Nguyen, Wanda

From: Nguyen, Wanda
Sent: Friday, April 28, 2017 2:03 PM
To: 'Robin Hume'
Subject: NDA 209401 CPX-351 -- FDA Information Request

Follow Up Flag: Follow up
Flag Status: Flagged

Good Afternoon Ms. Hume,

Regarding your submission dated March 31, 2017 for NDA 209401, we have the following clinical comments. Please respond to the comments with a point by point response.
Please respond via email by **3 PM on May 3, 2017**, followed with a formal submission to the NDA.

Non-hold Comments:

1) The ADSL dataset for Study 301 has 458 patients, although only 309 patients were randomized according to the CSR. While only 309 are flagged "Y" for the ITTFL variable, the remaining 149 patients do not appear to be screen failures, as under the SCRNFAIL variable, only 2 patients have "Y," and both of these patients are also flagged as being part of the ITT population. The IEVFL variable is similarly not helpful, as only 25 patients are labeled "Y," and these are all patients who are part of the ITT population as well. Please clarify the status of the 149 patients included in the ADSL dataset who are not part of the ITT population. Provide a response by May 3, 2017.

2) For Study 301: In the DM domain, it is unclear to what the variable RFENDTC refers. Other variables appear to reflect the randomization date (RFSTDTC), date of first study treatment (RFXSTDTC), date of last study treatment (RFXENDTC), date of end of study participation (RFPENDTC) , and date of death (DTHDTC), and these have correlates in the ADSL file , but RFENDTC has no interpretable computational algorithm (the one provided refers to a variable that was not provided in any of the other datasets, namely, RETPHDTC, and it does not correlate with any variable in the ADSL file). For at least some of the patients, this date is not that same as any of the other dates for the variables above. The same appears to be the case for study 205. Please provide clarification regarding this variable and its derivation for all relevant studies. Provide a response by May 3, 2017.

3) Please identify any differences in efficacy outcomes in the NDA submission that differs from the file submitted for the breakthrough designation request. Provide a response by May 3, 2017.

4) Please identify any differences in the data for Sites 002, 004 and 031 submitted 7/18/2016 to IND 072939 and in the current NDA. Provide a response by May 3, 2017.

Please respond via email by **3 PM on May 29, 2017**, followed with a formal submission to the NDA for the following comments.

Non-hold Comments:

5) At the pre-NDA meeting, you inquired (Question 9) as to whether Example 4 in the Integrated Summary of Safety (ISS) guidance was acceptable for this application. We responded "No, you will need to submit a full ISS that included includes detailed analysis of all available safety information." The ISS submitted in module 5.3.5.3 includes 1 page of text and 11,586 pages of tables and figures. We do not view the 1 page of text as fulfilling the requirement for an ISS. Submit an ISS by May 29, 2017.

6) At the pre-NDA meeting, we requested (response to question 5, FDA point 4) an integrated time-to-event data file for all subjects from studies 101, 204, 205, 206 and 301, with a set of minimum particular variables requested. This was submitted as the Tte data file in module 5.3.5.3, ISE, with an additional Dthroot data file. However, it is noted that patients in the Tte file do not have unique subject identifiers, so these data are uninterpretable (multiple subjects are included under many of the subject IDs, as subjects at different sites have the same subjid, and that is the only subject identifier included in this dataset). The same problem was identified in the RSinfo data file, also requested in our responses to the pre-NDA questions (question 5, FDA point 5). Please submit revised data files that include unique subject IDs for each subject by May 29, 2017.

Please confirm receipt of this notification.

Thank You,
Wanda

Comments to Sponsor

Wanda Nguyen, PharmD
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

10903 New Hampshire Avenue |Silver Spring, MD 20993
Wanda.Nguyen@fda.hhs.gov | 301-796-2808

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/s/

WANDA D NGUYEN
05/01/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209401

PROPRIETARY NAME ACKNOWLEDGEMENT

Celator Pharmaceuticals, Inc. (a Jazz Pharmaceuticals Company)
3180 Porter Drive
Palto Alto, CA 94304

ATTENTION: Robin L. Hume, MS, RAC
Senior Director, Regulatory Affairs

Dear Ms. Hume:

Please refer to your New Drug Application (NDA) dated and received March 31, 2017, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Cytarabine and Daunorubicin Injection, 100 mg and 44 mg.

We acknowledge receipt of your correspondence, dated and received March 31, 2017, requesting a review of your proposed proprietary name, Vyxeos.

If the application is filed, the user fee goal date for your proposed proprietary name review will be June 29, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact me in the Office of Surveillance and Epidemiology, at (240) 402-4845. For any other information regarding this application, contact Wanda Nguyen, Regulatory Project Manager, in the Office of New Drugs at (301) 796-2808.

Sincerely,

{See appended electronic signature page}

Neil Vora, PharmD, MBA, PMP
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

NEIL VORA
04/19/2017

Nguyen, Wanda

From: Nguyen, Wanda
Sent: Tuesday, April 18, 2017 11:44 AM
To: 'Robin Hume'
Subject: NDA 209401 CPX-351 (cytarabine and daunorubicin) liposome for injection--FDA Information Request

Good Morning Robin,

Regarding your submission dated March 31, 2017, for NDA 209401 CPZ-351 (cytarabine and daunorubicin) liposome for injection, we have the following information request.
Please respond to the information with a point by point response.
Please respond via email by **5pm on April 28, 2017,** followed with a formal submission to the NDA.

Information Request:

For Study CLTR0310-206:

1. Please Upload the ECG waveforms with annotations to the ECG warehouse (www.ecgwarehouse.com).
2. For PC.XPT dataset, some discrepancies between PCDTC and PCTPT (24 hour), PCTPTNUM (8) were found, the PC date didn't make sense, e.g. USUBJID = (b) (6).
3. For ADHOLTER.XPT dataset, please include ECG date of the averages, so it is easier to merge between ECG and PK data correctly.

Please confirm receipt of this notification.

Thank You,
Wanda

Wanda Nguyen, PharmD
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

10903 New Hampshire Avenue |Silver Spring, MD 20993
Wanda.Nguyen@fda.hhs.gov | 301-796-2808

U.S. FOOD & DRUG ADMINISTRATION

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/s/

WANDA D NGUYEN
04/18/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209401

NDA ACKNOWLEDGMENT

Celator Pharmaceuticals, Inc. (a Jazz Pharmaceuticals Company)
Attention: Robin L. Humes, MS, RAC
Senior Director, Regulatory Affairs
3180 Porter Drive
Palo Alto, CA 94304

Dear Ms. Humes:

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

Name of Drug Product: Vyxeos (cytarabine and daunorubicin) liposome for injection

Date of Application: March 31, 2017

Date of Receipt: March 31, 2017

Our Reference Number: NDA 209401

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 30, 2017, in accordance with 21 CFR 314.101(a).

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

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

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

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

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

If you have any questions, call me at (301) 796-2808.

Sincerely,

{See appended electronic signature page}

Wanda Nguyen, PharmD
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

WANDA D NGUYEN
04/05/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209401

ACKNOWLEDGE PRESUBMISSION

Celator Pharmaceuticals, Inc. (a Jazz Pharmaceuticals company)
Attention: Robin Hume, MS, RAC
Senior Director, Regulatory Affairs
3180 Porter Drive
Palo Alto, CA 94304

Dear Ms. Hume:

We have received the first section of your New Drug Application (NDA) under the program for step-wise submission of sections of a marketing application under 506 of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: (b) (4) (CPX-351 (100 mg cytarabine and 44 mg daunorubicin)) Lypsome Injection

Date of Submission: September 30, 2016

Date of Receipt: September 30, 2016

Our Reference Number: NDA 209401

Reference is also made to the General Correspondence received on February 03, 2017, under IND 72939 that contains the Rolling NDA Submission timeline.

We will review this presubmission as resources permit. Presubmissions are not subject to a review clock or to a filing decision by FDA until the application is complete.

Please cite the application listed above at the top of the first page of any communications concerning this supplemental application. Unless you are using the FDA Electronic Submissions Gateway (ESG), send all submissions by overnight mail or courier to the following address:

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

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

If you have any questions, call me at (301) 796-9304.

Sincerely,

{See appended electronic signature page}

Beatrice Kallungal, MS
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

BEATRICE A KALLUNGAL
03/27/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 072939

MEETING MINUTES

Celator Pharmaceuticals, Inc.
Attention: Lisa DeLuca, PhD.
Vice President, Regulatory Affairs
200 PrincetonSouth Corporate Center Suite 180
Ewing, NJ 08628

Dear Dr. DeLuca:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CPX-351, cytarabine and daunorubicin Liposome for Injection.

We also refer to the meeting between representatives of your firm and the FDA on July 13, 2016. The purpose of the meeting was to discuss the Chemistry, Manufacturing and Controls component for the upcoming CPX-351 (cytarabine:daunorubicin) liposome for injection NDA submission.

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

If you have any questions, call Rabiya Laiq, Pharm.D, Regulatory Business Process Manager at (240) 402-6153.

Sincerely,

{See appended electronic signature page}

Olen Stephens, Ph.D.
Quality Drug Product Reviewer, CMC
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes & Sponsor PowerPoint Slides

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: CMC

Meeting Date and Time: July 13, 2016 1:00 PM – 2:00 PM EST.
Meeting Location: WO Bldg. 22 Room 1309

Application Number: 072939
Product Name: CPX, 351, Cytarabine:Daunorubicin
Indication: Treatment of patients with Acute Leukemia
Sponsor/Applicant Name: Celator Pharmaceuticals, Inc.

Meeting Chair: Olen Stephens, Ph.D.
Meeting Recorder: Rabiya Laiq, Pharm.D.

FDA ATTENDEES
Rabiya Laiq, Pharm.D., Regulatory Business Process Manager
Jing Li, Ph.D., Biopharmaceutics Reviewer
Sherita McLamore-Hines, Ph.D., Quality Assessment Lead (Acting) CMC DHP
Derek Smith, Branch Chief (Acting) Office of Process & Facilities
Olen Stephens, Ph.D., Quality Drug Product Reviewer
Maotang Zhou, Branch Chief (Acting) Office of Process & Facilities

SPONSOR ATTENDEES

Lisa DeLuca	Vice President of Regulatory Affairs
Lawrence Mayer	President and Chief Scientific Officer
Les Mintzmyer	Vice President Manufacturing and Technical Operations
Sherwin Xie	Director of Analytical Research & Development
(b) (4)	Regulatory Consultant
(b) (4)	Regulatory Consultant
Kieron O' Donoghue	Director of CMC Regulatory Affairs (Jazz Pharmaceuticals)
William J. Bennett	Vice President of Biologics Development (Jazz Pharmaceuticals)

1.0 BACKGROUND

Purpose of meeting is to discuss the Chemistry, Manufacturing and Controls component for the upcoming CPX-351 (cytarabine:daunorubicin) liposome for injection NDA submission. Celator Pharmaceuticals, Inc. provided a meeting package outlining the proposed Chemistry, Manufacturing and Controls module content for the upcoming CPX-351 (cytarabine:

daunorubicin) liposome for injection NDA submission. FDA is providing the following feedback to streamline the NDA review. FDA sent Preliminary Comments to Celator on July 11, 2016.

2.0 DISCUSSION

Question 1: *Does FDA agree with Celator's proposed content plan for the Chemistry, Manufacturing, and Controls component of the NDA submission?*

FDA Response to Question 1:
The proposed CMC content for the forthcoming NDA submission appears reasonable, though FDA has the following comments that should be addressed in the original NDA submission:

A. Release specifications from the different drug substance vendors appear to exceed the respective USP/NF monograph in some cases. For the drug substance vendor specifications that exceed the corresponding monograph, provide a justification in the NDA that addresses whether the drug product acceptance criteria comply with the monograph or if the risk of the wider specifications is otherwise managed.

Meeting Discussion:

The sponsor confirmed that justification will be provided regarding the use of drug substance lots released from the DMF vendor that do not meet the current USP or NF monographs.

B. Provide quantitative results for reconstitution time in both the batch release and stability data.

Meeting Discussion:

The sponsor will provide quantitative reconstitution data as it is available. (b) (4) **and these constraints will be described in the original NDA submission.**

C. The stability protocol in Appendix H of the meeting package calls for a (b) (4) acceptance criteria of no more than (b) (4)%, whereas the release specifications are no more than (b) (4)%. Confirm that the current stability protocol has been tightened to the lower limit.

D. (b) (4)

Meeting Discussion:

The sponsor provided a justification [redacted] (b) (4) **The sponsor will detail this justification as well as provide reconciliation data of input and output values for individual lipids. This justification will be reviewed in the NDA.**

E. [redacted] (b) (4)

Meeting Discussion:

The sponsor outlined the manufacturing process [redacted] (b) (4) **The root cause of specific failed batches was discussed and the sponsor will include detailed description of those root causes as well as risk mitigation steps taken to develop a robust manufacturing process.**

F. In the original NDA submission include the following aspects regarding the lyophilization process development:

- [redacted] (b) (4)

G. Provide a detailed summary of the root cause(s) identified for the 3 failed drug product batches and describe the corrective actions.

Additional Biopharmaceutics Comments:

H. On face, the proposed in vitro drug release (IVR) method appears appropriate. However, note that the FDA does not perform a complete review of the in vitro drug release method

development report under a meeting's submission. Therefore, provide the IVR report under your future NDA submission.

Include the following in your future NDA submission:

- Provide the in vitro drug release data/profiles for the development studies in addition to the narrative summaries.
- The final proposed IVR method should be adequately validated. Include the narrative summaries and the in vitro drug release data/profiles for the conducted validation studies.
- A proposal for the IVR acceptance criteria, based on the overall data for the clinical and primary stability batches. Note that the FDA recommends a minimum of three specification time points covering the initial, middle, and final phases of the drug release profile. The proposed IVR acceptance criteria should be adequately justified in the NDA.
- (b) (4) You may provide the in vitro drug release data obtained using media representing a range of physiological conditions (e.g., whole blood, plasma, buffers with various pH's, stressed conditions, etc.).
- Additionally, please refer to the FDA's January 17, 2012, written responses (to questions submitted to this IND on July 22, 2011) for the FDA's comments on the IVR method. Please address each comment.

Additional Comments:

In the original NDA submission, the sponsor will clearly identify batches in the application that are intended for market, those batches that will not be marketed, and the justification for bridging the data for batches that will not be marketed. The sponsor will provide an IND amendment listing the intended commercial manufacturing sites for the NDA, including FEI numbers, contact information, addresses, and responsibilities of each site.

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/s/

RABIYA LAIQ
07/15/2016

OLEN M STEPHENS
07/15/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 072939

MEETING MINUTES

Celator Pharmaceuticals, Inc.
Attention: Lisa DeLuca, PhD
200 Princeton South Corporate Center
Suite 180
Ewing, NJ 08628

Dear Dr. DeLuca:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CPX-351 (cytarabine; daunorubicin) Liposome for Injection.

We also refer to the teleconference between representatives of your firm and the FDA on June 7, 2016. The purpose of the meeting was to discuss the need for a potential design of a Quantitative Pivotal Label Comprehension Study.

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

If you have any questions, call me, Alycia Anderson, Regulatory Project Manager, at (240) 402-4270.

Sincerely,

{See appended electronic signature page}

Donna Przepiorka, MD, PhD
Acting Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: A
Meeting Category: Guidance

Meeting Date and Time: June 7, 2016; 9:00 a.m. – 10:00 a.m. (ET)
Meeting Location: Teleconference

Application Number: IND 072939
Product Name: CPX-351 (Cytarabine; Daunorubicin) Liposome Injection
Indication: CPX-351 is being developed for use in the treatment of patients [redacted] (b) (b) (4)

Sponsor/Applicant Name: Celator Pharmaceuticals, Inc.

Meeting Chair: Donna Przepiorka, MD, PhD
Meeting Recorder: Alycia Anderson

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products
Donna Przepiorka, MD, PhD, Acting Clinical Team Leader
Alycia Anderson, Regulatory Project Manager

Office of Pharmaceutical Quality (OPQ)/Office of New Drug Products (ONDP)
Anamitro Banerjee, PhD, Branch Chief, Branch II, Division of New Drug Products I (DNDP I)
Sherita McLamore-Hines, PhD, Acting Quality Assessment Lead, Branch II, DNDP I

Office of Surveillance and Epidemiology/Division of Medication Error Prevention and Analysis
Lubna Merchant, PharmD, MS, Deputy Director
Yelena Maslov, PharmD, Team Leader
Hina Mehta, Acting Team Leader
Nicole Garrison, PharmD, Reviewer

SPONSOR ATTENDEES

Lisa DeLuca, PhD, Vice President Regulatory Affairs

Arthur Louie, MD, Chief Medical Officer
Michael Chiarella, Senior Director, Clinical Operations & Project Planning
[redacted] (b) (4)

1.0 BACKGROUND

[redacted] (b) (4)

The purpose of this teleconference is to discuss the need for a potential design of a Quantitative Pivotal Label Comprehension Study.

FDA sent Preliminary Comments to Celator Pharmaceuticals, Inc. on June 3, 2016.

2.0 DISCUSSION

Question 1:

Celator thinks that the two completed iterative qualitative studies provide adequate guidance to enable Celator to move forward [redacted] (b) (4) to describe the dosing strength of CPX-351 for labeling purposes. Does the FDA agree?

FDA Response to Question 1:

We do not believe that your studies have demonstrated that the "[redacted] (b) (4)" dose expressions are the best options to express the dose strength moving forward. The majority of survey questions were multiple choice. Questions that require participants to generate content on their own provide more reliable data to assess comprehension of the label options. As a result, we believe that the scores (or data) generated were biased due to the type of questions asked during the study. Despite our concern with the study method, our assessment of the data that you collected did not reach the same study conclusion [redacted] (b) (4) Additionally, we note that you revised the labeling, introductory text, and questionnaires for study 2, which could have contributed to different results [redacted] (b) (4) seen in study 2. Therefore not having all four options studied in formative study 2, we cannot determine [redacted] (b) (4) dose option. [redacted] (b) (4)

In addition, we do not agree with the use of the term [redacted] (b) (4)" in reference to the dosing strength of CPX-351. See the response to question #2.

We recommend that you further evaluate the best labeling option and design a validation label comprehension study using dosing based on the mass (mg/m^2) of each individual

component or dosing based on mass (mg/m^2) of daunorubicin only. The study questions should be designed without introducing bias, such that the study results clearly demonstrate how the final labeling can be further optimized.

Discussion:
The Sponsor proposed to base dosing instructions and strength on the mass (i.e., mg/m^2, mg, etc.) for both cytarabine and daunorubicin content individually, [redacted] (b) (4)

FDA agreed with this plan. FDA recommended the Sponsor submit the proposed dosing section of the PI and container labels for our review prior to conducting the label comprehension study.

Question 2:
Celator would like to move forward with [redacted] (b) (4) **for the draft labeling to be included with the NDA. Does FDA agree that Celator can proceed with the term** [redacted] (b) (4) **in reference to CPX-351 dosing strength?**

FDA Response to Question 2:
As previously communicated, the strength must be based on each active ingredient in the combination product and should be expressed in mg per vial for each ingredient. We do not agree with the use of the terms [redacted] (b) (4) or [redacted] (b) (4) in reference to the dosing strength of CPX-351.

Discussion:
No discussion occurred.

Question 3:
If FDA requires that Celator conduct a pivotal quantitative label comprehension study, does FDA agree on the design of the study as put forth Section 2.3.1?

FDA Response to Question 3:
Please see our response to question 1. Your labeling comprehension study protocol is designed as a comparative study instead of a validation label comprehension study. Your labeling comprehension study should be designed to focus on the best labeling option (once that is identified from formative testing) and be able to demonstrate that representative users can understand the dosing information and dosing calculations in order to prepare the product safely.

Discussion:
FDA confirmed that the validation label comprehension study would be the pivotal study; however, FDA emphasized that the study should focus on the best labeling option rather than being comparative, and that the study should utilize "real world" scenarios to demonstrate that representative users can understand the dosing information and dosing calculations in order to prepare the product safely.

The Sponsor described their plan to include 100 subjects with 3 cohorts by professional background (b) (4) *FDA disagreed* (b) (4) *The Sponsor indicated they could submit revised documents as well as the draft labels and prescribing information to the IND in about 2 weeks, and that they planned to start the study in early August. FDA agreed to review the revised protocol in a timely manner.*

The Sponsor also articulated their plan to submit the NDA on August 31. Given the delayed start of the label comprehension study, the Sponsor asked if they could submit the study report after the NDA submission. FDA agreed to accept the study report no later than 30 days after receipt of the NDA.

3.0 OTHER IMPORTANT MEETING LANGUAGE

PREA REQUIREMENTS

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

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

FDA agreed to provide review comments on the revised protocol and questionnaire as soon as feasible following its submission to the IND.

5.0 ACTION ITEMS

There are no actions items at this time.

6.0 ATTACHMENTS AND HANDOUTS

Celator Pharmaceuticals, Inc. did not provide any slides or handouts for this teleconference.

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

/s/

DONNA PRZEPIORKA
06/15/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 072939

GRANT –
BREAKTHROUGH THERAPY DESIGNATION

Celator Pharmaceuticals, Inc.
Attention: Lisa DeLuca, PhD
Vice President, Regulatory Affairs
200 Princeton South Corporate Center
Suite 180
Ewing, NJ 08628

Dear Dr. DeLuca:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CPX-351 (Cytarabine: Daunorubicin) Liposome Injection.

We also refer to your March 23, 2016, request for Breakthrough Therapy designation and the amendment submitted April 22, 2016. We have reviewed your request and have determined that CPX-351 (Cytarabine: Daunorubicin) Liposome Injection for the "*treatment of adults with therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC)"* meets the criteria for Breakthrough Therapy designation. Therefore, we are granting your request for Breakthrough Therapy designation. Please note that if the clinical development program does not continue to meet the criteria for Breakthrough Therapy designation, we may rescind one or both designations.

FDA will work closely with you to provide guidance on subsequent development of CPX-351 (Cytarabine: Daunorubicin) Liposome Injection for the "*treatment of adults with therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC)"* to help you design and conduct a development program as efficiently as possible. For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics.*[1]

When breakthrough therapy designation is granted, sponsors are asked to submit a Type B meeting request for a multidisciplinary comprehensive discussion of the drug development program, including planned clinical trials and plans for expediting the manufacturing

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

development strategy. Please refer to MAPP 6025.6 - *Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics,* Attachment 1, for potential topics for discussion at this initial breakthrough therapy meeting[2].

We note your recent Pre-New Drug Application meeting held on May 16, 2016 submitted on March 10, 2016. At this point in your drug development program, holding the initial breakthrough therapy meeting is not necessary. However, please contact the Regulatory Project Manager noted below to determine if any information is required at this time to expedite the review of your breakthrough designated product.

If the breakthrough therapy designation for CPX-351 (Cytarabine: Daunorubicin) Liposome Injection for the "*treatment of adults with therapy-related AML (t-AML), or AML with myelodysplasia-related changes (AML-MRC)"* is rescinded, submission of portions of the NDA will not be permitted under this program. However, if you have Fast Track designation you will be able to submit portions of your application under the Fast Track program.

If you have any questions, contact Alycia Anderson, Regulatory Project Manager, at (240) 402-4270.

Sincerely,

{See appended electronic signature page}

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

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[2] http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm.

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

/s/

ANN T FARRELL
05/17/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 072939

MEETING MINUTES

Celator Pharmaceuticals, Inc.
Attention: Lisa DeLuca, PhD
200 Princeton South Corporate Center
Suite 180
Ewing, NJ 08628

Dear Dr. DeLuca:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CPX-351 (Cytarabine; Daunorubicin) Liposome Injection.

We also refer to the meeting between representatives of your firm and the FDA on May 16, 2016. The purpose of the meeting was to discuss a Pre NDA and to discuss the data from the Phase 3 trial and any outstanding issues from the EOP2 meeting, and format of the NDA.

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

If you have any questions, call me, Alycia Anderson, Regulatory Project Manager at (240) 402-4270.

Sincerely,

{See appended electronic signature page}

Donna Przepiorka, MD, PhD
Acting Clinical Team Lead
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	May 16, 2016, 9:00 a.m. – 10:00 a.m. (ET)
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1311 Silver Spring, Maryland 20903
Application Number:	IND 072939
Product Name:	CPX-351 (Cytarabine; Daunorubicin) Liposome Injection
Indication:	CPX-351 is indicated for the treatment of patients with acute myeloid leukemia (AML).
Sponsor/Applicant Name:	Celator Pharmaceuticals, Inc.
Meeting Chair:	Donna Przepiorka, MD, PhD
Meeting Recorder:	Alycia Anderson, CCRP

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products
Donna Przepiorka, MD, PhD, Acting Clinical Team Leader
Aviva Krauss, MD, Clinical Reviewer
Ashely Ward, MD, Clinical Reviewer
Bindu Kanapuru, MD, Clinical Reviewer
Theresa Carioti, MPH, Chief, Project Management Staff
Alycia Anderson, Regulatory Project Manager

OHOP/Division of Hematology Oncology Toxicology
Christopher Sheth, PhD, Pharmacology/Toxicology Team Leader
Michael Manning, PhD, Pharmacology/Toxicology Reviewer

Office of Clinical Pharmacology/Division of Clinical Pharmacology V
Bahru Habtemariam, PharmD, Clinical Pharmacology Team Leader
Olanrewaju Okusanya, PharmD, MS, Clinical Pharmacology Reviewer

Office of Pharmaceutical Quality(OPQ)/Office of New Drug Products (ONDP)
Anamitro Banerjee, PhD, Branch Chief, Branch II, Division of New Drug Products I (DNDP I)
Nina Ni, PhD, Product Quality Reviewer

SPONSOR ATTENDEES

Lisa DeLuca, Vice President of Regulatory Affairs
Scott Jackson, Chief Executive Officer
Lawrence Mayer, President and Chief Scientific Officer
Les Mintzmyer, Vice President Manufacturing and Technical Operations
Arthur Louie, Chief Medical Officer
Michael Chiarella, Senior Director, Clinical Operations & Project Planning
Sherwin Xie, Director of Analytical Research & Development
Antje Hoering, CEO Cancer Research and Biostatistics
(b) (4), Regulatory Consultant
(b) (4), Clinical Pharmacology Consultant

1.0 BACKGROUND

CPX-351 (Cytarabine; Daunorubicin) Liposome Injection is proposed for the treatment of patients with acute myeloid leukemia (AML).

The purpose of this face-to-face meeting is to discuss the data from the Phase 3 trial, any outstanding issues from the EOP2 meeting, and format of the planned NDA.

FDA sent Preliminary Comments to Celator Pharmaceuticals Inc. on May 12, 2016.

2. DISCUSSION

2.1.

Question 1:
Based on previous guidance by FDA, Celator believes that the CPX-351 clinical data provided with the NDA filing plus the historical literature describing the use of cytarabine and daunorubicin in combination as well as the non-clinical studies demonstrating the contribution of both agents to the overall therapeutic effect of CPX-351 will be sufficient to fulfill the requirements for the combination rule.

While these components will be individually included in their respective sections of the NDA filing, should the combination rule be specifically addressed separately (combining the relevant clinical, non-clinical and literature information) within the NDA filing, if so please provide the location (NDA Section)?

FDA Response to Question 1:
The overview of the data that established the need for the use of the combination in your product can be provided in the Clinical Overview (Module 2.5) Section 2.5.1. Whether these data will be sufficient to fulfill the requirement for the combination rule will be a review issue.

Should you wish to provide any other information regarding the combination rule, it can be included in the cover letter section (m1.2), as a separate document from the cover letter, with a clear leaf title.

Discussion:
No discussion occurred.

Question 2:
Does FDA have any comments to provide regarding the design of the quantitative study (protocol submitted separately from pre NDA Meeting briefing material)?

FDA Response to Question 2:
We will discuss this in a separate Type A meeting as requested in the meeting package submitted on May 6, 2016.

Discussion:
No discussion occurred.

Question 3:
Celator will provide the study report for the label comprehension study in Section 1.14.1.4 of the NDA, is that acceptable?

FDA Response to Question 3:
We will discuss this in a separate Type A meeting as requested in the meeting package submitted on May 6, 2016.

Discussion:
No discussion occurred.

Question 4:
Celator understands Bioresearch Monitoring (BIMO) data is required within the NDA filing and BIMO will be provided. However, Celator respectfully requests specific guidance from the Division on the full contents of the BIMO package. Does the Agency require the clinical site listings only or the listings along with datasets and reviewer's guide?

FDA Response to Question 4:
For additional information about Summary Level Clinical Site Data that should be submitted in the NDA, please see:
http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf
Additional site-specific information may be requested following review of the material submitted in the NDA.

Discussion:
No discussion occurred.

Question 5:
Does FDA agree that provision of the clinical data, as outlined in Appendix F, is acceptable for filing?

FDA Response to Question 5:
The acceptability of the submission content for filing will be a review issue that cannot be determined at this time.

We also have the following comments:

1. As the data sets to be integrated for the ISS consist of various studies that took place over a number of years, some of which are legacy studies, please make sure that the integrated data set uses a uniform CTCAE grading and event terms according to the same MedDRA version.

2. Please note that case report forms should be submitted in the Clinical Study Report in addition to the individual patient listings (data sets), rather than in a separate section of the eCTD, as proposed in section 6.3 (page 28) of the meeting package. Please see: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073113.pdf

3. The integrated safety data sets should include at least adverse events, demographics, baseline disease information, medical history, concomitant medications, exposure, clinical laboratory tests, and vital signs. Please include also the epoch and cycle number (induction 1, induction 2, consolidation 2, etc.) for each adverse event.

4. Please include an integrated time-to-event data file for all subjects from studies 101, 204, 205, 206 and 301, with at least the following information: study identification number, site identification number, subject number, treatment arm, demographic information, date of first study drug dose, date of CR, date of relapse, date of transplantation, if performed after CPX-351/7+3, date of last contact, status at last contact (alive, dead or lost), proximate cause of death, and root cause of death as determined by the sponsor (e.g. active AML, treatment-related, intercurrent illness, etc.). For all deaths on study within 30 days of the last dose of study drug, when the cause of death is listed as disease-related, ensure that the narrative clearly describes the data showing active leukemia.

Discussion:
The Agency clarified that the root cause of death analysis by the Sponsor is derived and they did not expect the information verbatim in source documentation.

5. Please include a simple data file that identifies the tests used to determine response on CLTR0310-301 and CLTR0308-205. This should include at least the following variables: study identification number, site identification number, subject identifier, disease subtype (t-AML, MDS-treated, MDS untreated etc.), date of first dose of study drug, response category (i.e., CR, CRi, etc.), date of response, cycle (induction 1, induction 2, etc.) and

day of response, date of marrow used to identify response, date of ANC used to identify response, and date of platelet count used to identify response.

6. For Study 204, please clarify how you will code for patients who crossed over from the control arm to the CPX-351 arm in your safety and efficacy datasets.

7. With regard to your proposed table of contents (Appendix G), please see: http://www.fda.gov/downloads/drugs/developmentapprovalprocess/formssubmissionrequirements/electronicsubmissions/ucm163175.pdf for the current eCTD table of contents. We also note that the CSR for your pivotal study CLTR0310-301 is missing from your proposed TOC.

8. Please refer to the Additional Clinical Pharmacology Comments below for our expectations for the submission of population PK and exposure-response analysis reports, results, and datasets.

Discussion:
No discussion occurred.

Question 6:
Does FDA agree that cytarabine and daunorubicin are the appropriate reference listed drugs?

FDA Response to Question 6:
You state in your meeting package that you intend to rely, in part, on published literature describing the use of cytarabine and daunorubicin in combination to fulfill the requirements of the combination rule. You also state that you intend to "reference the labels to cytarabine and daunorubicin" to support, in part, nonclinical requirements. Please note that referring to information in the labeling of listed drug(s) constitutes reliance on FDA's finding of safety and/or effectiveness for those listed drugs.

If you intend to rely, in part, on information that is necessary for approval that comes from studies not conducted by you or for you (e.g., FDA's finding of safety and/or effectiveness for a listed drug(s); published literature) and for which you have not obtained a right of reference, your proposed NDA will be a 505(b)(2) application. You must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You will need to identify the specific listed drug(s) upon which you propose to rely (i.e., NDA numbers) and establish a "bridge" (e.g., via comparative bioavailability data) between your drug product and each listed drug to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. Specifically, you should identify the specific drug product used in the cited studies and explain why the activity of that drug product can be used as evidence of the activity of your

product. You should include a copy of such published literature in your NDA and identify any listed drug(s) described in the published literature (e.g., trade name(s)).
FDA does not typically advise a sponsor on the selection of a particular listed drug(s) that may be relied upon to support approval of a proposed product. A sponsor interested in submitting a 505(b)(2) application that relies upon FDA's finding of safety and/or effectiveness for a listed drug(s) should determine which listed drug(s) is/are the most appropriate for their development plan.

For additional information about submitting a 505(b)(2) application, refer to the 505(b)(2) Regulatory Pathway section below.

Discussion:
The Sponsor asked whether by referencing Daunoxome and Depocyte, that would be considered referencing information for free daunorubicin and cytarabine drug product. The Agency agreed.

Question 7:
Does the FDA agree that post marketing safety surveillance of CPX-351 can be accomplished according to CFR314.80, and that a formal REMS program is not required?

FDA Response to Question 7:
At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.

Discussion:
No discussion occurred.

Question 8:
Does FDA agree with Celator's plan not to include an ISE in the NDA filing?

FDA Response to Question 8:
Your proposal to submit a SCE in lieu of a full ISE is acceptable if the comprehensive review and analyses can be included within the space limitations of the SCE. For more information on when the SCE can serve as the ISE, see the FDA Guidance for Industry on the Integrated Summary of Effectiveness, which can be found at:
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079803.pdf

Discussion:
No discussion occurred.

Question 9:
For a 505(b)(2) NDA filing, is following Example 4 set forth in the *Guidance for Industry, "Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document"* acceptable for the ISS?

FDA Response to Question 9:
No. You will need to submit a full ISS that includes detailed analyses of all available safety information.

Discussion:
No discussion occurred.

Question 10:
Is it acceptable for Celator to provide a summary of these data in the ISS and include it in the Summary of Clinical Pharmacology Studies (NDA Module 2, Section 2.7.2)?

FDA Response to Question 10:
Yes. You should also include a detailed description and discussion of the impact of renal impairment on the clearance of CPX-351 and copper in the study report along with all relevant study tables, figures and associated datasets in Module 5.

Discussion:
No discussion occurred.

Question 11:
In order to support labeling for "USE IN SPECIAL POPULATIONS" – Geriatric Use, Celator intends to pool the safety data for patient 65 years of age and older from the Phase I, II, and III studies. Is the ISS the appropriate location within the NDA filing to present these data?

FDA Response to Question 11:
Yes, the ISS is the appropriate location for subpopulation analyses of pooled safety data.

Discussion:
No discussion occurred.

Question 12:
Will FDA agree to allow the submission of a minor amendment (not later than 30 days after the NDA submission) containing the required 3 months stability data, at storage temperature and accelerated conditions, for CPX-351 drug product manufactured with the APIs from the new suppliers?

FDA Response to Question 12:
Your proposal is acceptable. However, the comments provided in the March 01, 2016 correspondence were made with the assumption that the cGMP issues with (b) (4) will be satisfactorily resolved. If you propose to use stability data generated using drug

substances sourced from [redacted] as the primary stability data in the NDA (please see our response to Question 3 in the CMC Meeting dated March 02, 2016), provide adequate data for these drug substance lots as indicated in our response. This issue may be further discussed during the meeting. Some of the stability data may be provided within 30 days of submission.

Discussion:
No discussion occurred.

Question 13:
Celator will also have release data for Conformance Batch 2 at time of NDA submission. Conformance Batch 2 will be produced using alternate supplier APIs. Would the FDA like Celator to update the NDA submission with minor submissions for additional stability data as it becomes available (stability time points are 3, 6, 9, 12, 18, 24, 30, 36, 42, and 48 months). Given this schedule stability data for 3 months will be available during the review.

FDA Response to Question 13:
See response to Question 12. You may provide updated stability data during the review if available.

Discussion:
No discussion occurred.

Question 14:
If all other aspects of the NDA are deemed acceptable to approve, would FDA consider [redacted]?

FDA Response to Question 14:
No, in accordance with 21 CFR 314.125(b)(13) and Section 505(d)(3) of the Act, the FDA cannot approve an NDA where the facilities and controls are found inadequate. Therefore, all facilities must be CGMP compliant prior to approval of the NDA [redacted]

Discussion:
No discussion occurred.

Question 15:
Will FDA accept a CMC supplement in support of [redacted] as a Changes Being Effected (CBE) submission (post approval)?

FDA Response to Question 15:
No, the [redacted] is not considered as a CBE change as per the *Guidance for Industry: Changes to an Approved NDA or ANDA*.

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm077097.pdf

(b) (4) Thus, a PAS (prior approval supplement) is required.

Discussion:
No discussion occurred.

Question 16:
Celator intends to have 4 CPX-351 batches available for commercial launch. These include Conformance Batch 1 (manufactured with (b) (4) API material), Conformance Batches 2 and 3 (both manufactured with alternative API supplied material, and the full GMP batch manufacture in April 2016 with the alternative API supplied material. Does FDA agree with this plan?

FDA Response to Question 16:
Your proposed Conformance Batch 1 may not be used as commercial batch due to the cGMP violations of the drug substance manufacturing site at this time. Conformance Batches 2 and 3 may be used as commercial batches as long as the batches meet both specification and cGMP requirements.

Discussion:
No discussion occurred.

Question 17:
It is Celator's intent to (b) (4) . Is this approach for the NDA acceptable?

FDA Response to Question 17:
No. Your product label should contain sufficient information to allow the prescriber use your drug safely and effectively. You will need to include any relevant drug-drug interactions to the conventional forms of daunorubicin and cytarabine in your label.

Discussion:
No discussion occurred.

Question 18:
Given FDA's previous response that no additional nonclinical reproductive studies are required, it is Celator's intent to reference the labels to cytarabine and daunorubicin for the NDA submission on this topic with no additional reference to published literature. Is this approach for the NDA acceptable?

FDA Response to Question 18:
The approach is acceptable, but not complete. Provide in the NDA an assessment of potential combined effects of CPX-351, on fertility, embryofetal and pre- and post natal development to facilitate the review.

Discussion:
The Sponsor asked for clarity on the nature of the reproductive and developmental toxicology assessment of their product. The Agency clarified that the Sponsor should research the respective contributions of each molecule to the toxicity of their product using literature and information in the labels. The Sponsor agreed.

Question 19:
Celator has worked closely with clinical sites in an effort to conduct a study in hepatic impaired patients. Despite this effort the clinical sites have failed to enroll a single patient in over a year of the study initiation. Given this, Celator is requesting to be released from the requirement to conduct a study in hepatic impaired patients for NDA filing. Does FDA agree that the CPX-351 NDA submission can be filed without the inclusion of data from hepatic impaired patients treated with CPX-351?

FDA Response to Question 19:
Yes. It is the agency's expectation that the NDA submission should be complete at the time of original NDA submissions; however, the FDA acknowledges the challenge the sponsor has faced in recruiting patients with hepatic impairment based on Child-Pugh score. Given that the dose of non-liposomal daunorubicin is adjusted based on bilirubin levels, you should consider evaluating patients with bilirubin levels < 1.2 mg/dL, 1.2 to 3 mg/dL, or > 3 mg/dL. This will be useful in determining if any dose adjustment similar to daunorubicin is necessary for CPX-351. For clinical pharmacology studies that cannot be completed prior to NDA submission, appropriate restrictions should be included in proposed labeling.

Discussion:
No discussion occurred.

Question 20:
In order to provide information for Section 8.0 "USE IN SPECIAL POPULATIONS - HEPATIC IMPAIRMENT" of the Package Insert, (b) (4) . Is this approach acceptable?

FDA Response to Question 20:
No. The daunorubicin label proposes a dose adjustment based on bilirubin levels as stated below
"Patients with serum bilirubin concentrations of 1.2 to 3 mg/dL should receive 75% of the usual daily dose and patients with serum bilirubin concentrations greater than 3 mg/dL should receive 50% of the usual daily dose. "
You have not provided any data supporting such dose adjustment for your drug. In addition, given that it is a fixed combination, a reduction in daunorubicin amount will result in a

reduction in cytarabine as well, for which there are no recommended dose adjustments in the current product label.

Discussion:

No discussion occurred.

Additional Comments:

Clinical:

1. Although your orphan designation for the AML indication exempts you from the Pediatric Research Equity Act (PREA) requirements, we encourage you to evaluate CPX-351 in children and submit a Proposed Pediatric Study Request (PPSR) if such an investigation is designed to generate informative data.

2. Please ensure that your proposed prescribing information is consistent with the Pregnancy and Lactation Labeling Rule (see the section Prescribing Information below).

Statistical:

1. Provide all SAS programs that were used to create all of the efficacy and safety tables and figures included in the main text portion of the CSR. Please also provide all necessary macros and SAS utility programs. All programs should be thoroughly commented and have passed Sponsor's validation procedures.
    - Ensure the SAS dataset file names are consistent with those in the SAS programs that call them, so that the Agency can run the programs smoothly to verify the results/figures/tables reported in the submission.
    - Annotations for all efficacy and safety tables and figures should be included in the main text portion of the CSR. The annotations should indicate which analysis dataset variables were used to produce the tables or figures.

Discussion:

The Agency clarified that the annotation specifically should identify the program used to generate the table. This should apply to all studies required to support labeling for efficacy.

Clinical Pharmacology:

1. In your NDA submission, you should address the following questions in the Summary of Clinical Pharmacology:

    a. What is the basis for selecting the doses and dosing regimen used in the trials completed to support a marketing application? Identify individuals requiring dose modifications, time to the first dose modification and reason for the dose modification in support of the proposed dose and administration.
    b. What are the exposure-response relationships for efficacy, safety and biomarkers?
    c. What is potential for CPX-351 to prolong the QT/QTc interval?
    d. What are the characteristics of distribution and elimination?

e. What influence do extrinsic and intrinsic factors (such as sex, race, weight and disease) have on exposure, efficacy, or safety? What dose modifications are recommended?

Discussion:
The Sponsor requested clarification regarding the Agency's expectations for assessment of the exposure-response relationships. The Agency agreed that due to differences in measures of response, the evaluations for patients with relapsed disease could be separated for untreated disease.

The Agency recommended that safety analyses should be conducted using all of the available data and provided a discussion of strategies for analyses that might affect labeling. The Agency also recommended that the Sponsor conduct integrated dose-response analyses for safety and activity using study 101 data as part of the dose justification assessment.

The Sponsor clarified that they had no special biomarkers for biomarker analyses.

2. You should apply the following advice in preparing the clinical pharmacology sections of the original submission:

   a. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.
   b. Provide final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with minimum and maximum values as appropriate.
   c. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.
      - Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
      - Identify individual subjects with dose modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dose modifications in the datasets.
   d. Submit the following for the population pharmacokinetic analysis reports:
      - Standard model diagnostic plots
      - Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line
      - Model parameter names and units in tables.
      - Summary of the report describing the clinical application of modeling results.

Refer to the following pharmacometric data and models submission guidelines http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm.

e. Submit the following information and data to support the population pharmacokinetic analysis:
   - SAS transport files (*.xpt) for all datasets used for model development and validation
   - A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets
   - Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submitted these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt)

f. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and toxicity) relationships in the targeted patient population. Refer to Guidance for Industry found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf and http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf.

Discussion:
No discussion occurred.

Post Meeting Addendum:
The Agency would like to inform Celator Pharmaceuticals, Inc. that the drug product is a lyophilized liposome dispersion containing two API's in a fixed molar ration. Therefore, this application will not be under the PDUFA V Program as CPX-351 is not considered a new molecular entity.

3.0 OTHER IMPORTANT MEETING LANGUAGE

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017,** the following submission types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g., trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication X*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

FDA has made a preliminary determination that the application for this would not be reviewed as a new molecular entity (NME) and would not be subject to the Program under PDUFA V.

Please note that this is a preliminary determination, based on information available to FDA at this time, and will be re-evaluated at the time your application is submitted. This determination is based on our understanding of the active moiety (21 CFR 314.108(a)) and whether another marketing application containing the same active moiety is approved or marketed. Please also note that the NME determination for an application is distinct from and independent of the new chemical entity (NCE) determination and any related exclusivity determinations, which are made after approval of an NDA.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site

b. Number of subjects randomized at each site
c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

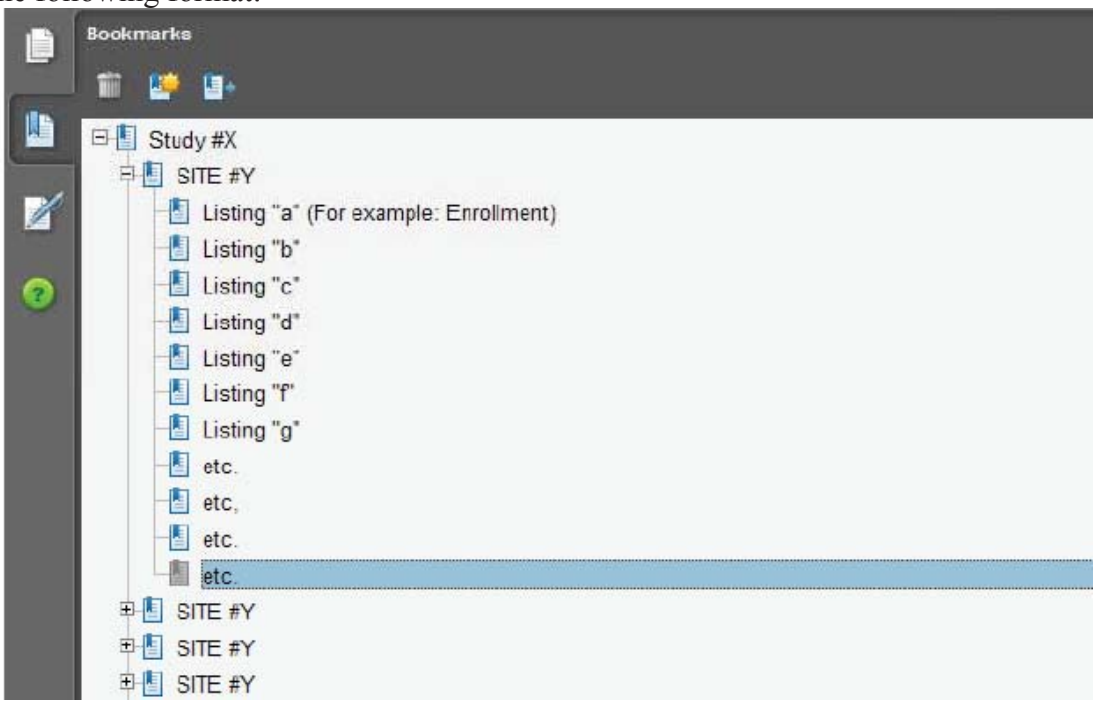
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)

j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into

this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There are CMC questions that were not discussed during this meeting, but will be addressed in the CMC Type A meeting that was submitted on May 17, 2016. The pre NDA CMC-only meeting is planned for July 7, 2016.

5.0 ACTION ITEMS

There are no action items.

6.0 ATTACHMENTS AND HANDOUTS

Celator Pharmaceuticals Inc. did not provide the Agency with handouts or slides for this meeting.

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

/s/

DONNA PRZEPIORKA
06/01/2016

CDER Breakthrough Therapy Designation Determination Review Template

IND/NDA/BLA #	IND 072939
Request Receipt Date	3/23/2016
Product	CPX-351 (cytarabine:daunorubicin) Liposome Injection
Indication	CPX-351 is indicated for the treatment of adults with therapy-related AML (t-AML), or AML with myelodysplasia-related changes (AML-MRC)
Drug Class/Mechanism of Action	Liposomal formulation of a fixed combination of the the antineoplastic drugs cytarabine and daunorubicin
Sponsor	Celator Pharmaceuticals
ODE/Division	OHOP/DHP
Breakthrough Therapy Request Goal Date (within 60 days of receipt)	5/22/2016

Note: This document should be uploaded into CDER's electronic document archival system as a clinical review and will serve as the official Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Note: Signatory Authority is the Division Director.

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.*Section I to be completed within 14 days of receipt for all BTDRs*

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

CPX-351 (cytarabine:daunorubicin) Liposome Injection is indicated for the treatment of adults with therapy-related AML (t-AML), or AML with myelodysplasia-related changes (AML-MRC).

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

3. **Consideration of Breakthrough Therapy Criteria:**

a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

If 3a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequeate and sufficiently complete to permit a substantive review?

- ☒ YES the BTDR is adequate and sufficiently complete to permit a substantive review
- ☐ Undetermined
- ☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:

If 3b is checked "No", BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If 3b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

5. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

6. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

- *Information regarding the disease and intended population for the proposed indication.*
- *Disease mechanism (if known) and natural history (if the disease is uncommon).*

The standard therapy for newly diagnosed patients with acute myeloid leukemia (AML) is intensive induction therapy with a combination of cytarabine for 7 days and an anthracycline (such as daunorubicin or idarubicin) for 3 days, the so-called "7+3" regimen (Dombret and Gardin 2016). The doses and schedules of these drugs for treatment of AML were determined empricially after very limited dose-finding studies. CPX-351 is a liposomal formulation of a fixed combination of cytarabine and daunorubicin in a 5:1 molar ratio within the liposome. Table 1 below shows a comparison of dose delivery by CPX-351 vs 7+3.

[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

Table 1. CPX-351 vs 7+3

	CPX-351 (1 unit = 1.00 mg cytarabine and 0.44 mg daunorubicin) 90 minute infusion on days 1, 3, and 5	"7 +3" Cytarabine – 7 day continuous infusion Daunorubicin – IV push on Days 1, 2, and 3
Cytarabine	• 100 mg/m^2 x 3 days • Total = 300 mg/m^2	• 100 mg/m^2 x 7 days • Total = 700 mg/m^2
Daunorubicin	• 44 mg/m^2 x 3 days • Total = 132 mg/m^2	• 60 mg/m^2 x 3days • Total = 180 mg/m^2

The 5:1 molar ratio of the cytotoxics in CPX-351 is based on in vitro data that the ratio of combination therapy is crucial to efficacy, as certain ratios lead to synergistic effects of the various agents, whereas other ratios lead to antagonism and subsequent loss of therapeutic effect (Mayer 2006, Harasym 2010 and others). In vivo, the ratios of the two drugs at the target can't be controlled tightly when the drugs are given independently. In CPX-351, the drugs are encapsulated in a liposomal formulation at a fixed ratio for delivery to the target in order to optimize synergy for the treatment of AML.

A number of clinical, cytogenetic and molecular factors have been identified that are prognostic for AML disease control and survival. Patients with AML occuring after antecedent chemo- or radiation therapy (therapy-related AML (t-AML)), or AML with myelodysplasia-related changes (AML-MRC) that evolved from other hematologic conditions (such as after MDS, after MDS/MPN, or with MDS-related cytogenetic changes; sometimes referred to as secondary AML) have a prognosis that is worse than patients with de novo AML (Granfeldt Ostgard 2015, Hulegardh 2015, Leith 1997). Due to the expected chemoresistant nature of these types of AML, patients with t-AML or secondary AML are frequently excluded from clinical trials of new drugs for the treatment of AML.

7. Information related to endpoints used in the available clinical data:

a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

Trial CLTR0310-301 is a recently completed Phase III trial in which patients with newly-diagnosed t-AML or secondary AML between the ages of 60 and 75 years were randomized to receive CPX-351 or standard 7+3.

The primary endpoint used to support the BTDR is overall survival (OS), which was the primary endpoint of the study. Supportive evidence is provided by the secondary endpoints, including post-induction response rate, specifically complete remission (CR) rate, CR + complete remission with incomplete hematologic recovery rate (CRi), and event-free survival (EFS).

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

- *A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).*

- *A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).*

- *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.*

OS is a clinical endpoint that directly measures clinical benefit in AML, and that can be used to support regular approval. There are no established surrogate endpoints to support approval in AML.

Durable complete remission (CR) is the endpoint that DHP considers reasonably likely to predict clinical benefit in AML, and that might potentially support accelerated approval in AML.

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

None that were assessed in the trial used to support this request.

8. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

- *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*

- *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

Table 2 below summarizes FDA-approved therapies for patients with AML. No new drugs have been approved since 1990.

Table 2. Available therapies for patients with newly diagnosed AML

Drug	Class	Indication	Approval	Treatment effect
Cytarabine	Pyrimidine analog	In combination with other approved anticancer drugs for remission induction in ANLL of adults and children	1969	CR rate in combination with daunorubicin: 53-65%* **from the daunorubicin PI*
Daunorubicin	Anthracycline	In combination with other approved anticancer drugs for remisison induction in ANLL of adults	1979	CR rate: Single agent in ANLL:40-50% In combination with cytarabine: 53-65%
Mitoxantrone	Topoisomerase inhibitor	In combination with other approved drug(s) in the intial therapy of acute nonlymhocytic leukemia in adults (ANLL), including AML.	1987	CR rate 63% vs 53% (compared to daunorubicin) Median survival 312 days vs 230 days

Idarubicin	Anthracycline	In combination with other approved antileukemic drugs for the treatment of AML in adults	1990	Compared to daunorubicin: *Study 1*: CR rate- 78% vs 58% Median survival 508 vs 435 days *Study 2*: CR rate- 67% vs 58% Median survival 393 days vs 281 days

As noted above, standard of care for newly diagnosed patients who are deemed candidates for intensive chemotherapy is to receive these agents in combination. The most commonly used regimens are variations of the 7+3 regimen referred to above, using a combination of cytarabine with an anthracycline. In a registry study, the CR rates were 37%-53% for patients ≥65 years old with t-AML or secondary AML treated with intensive chemotherapy (Hulegardh 2015). CR rates in patients over 60 with secondary AML have been reported to range from 45-52%, with 2-year OS of about 22% (Lowenberg 2009).

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[3].

Volasertib, a Polo-like kinase 1 (PLK1) inhibitor was granted Breakthrough Therapy Designation on 06/17/2013 for use in combination with low dose cytarabine (LDAC), for the treatment of adult patients ≥65 years with previously untreated AML who were considered ineligible for intensive remission induction therapy. Breakthrough Therapy Designation was supported by an increased complete remission rate (CR+CRi) of 31% compared to 13% for cytarabine alone in a phase 2 trial of 87 patients with AML who were deemed ineligible for standard intensive induction therapy. Median OS was 8 months on the volasertib arm compared with 5.2 months with cytarabine alone. Of note, the pivotal phase three trial for this indication (1230.14/POLO-AML-2), in which patients ≥ 65 years of age with untreated AML who were ineligibile for intensive induction therapy (b) (4)

Midostaurin, a small molecule inhibitor of multiple tyrosine kinases including Fms-like tyrosine kinase 3 (FLT3), was granted Breakthrough Therapy Designation on 1/29/2016 for the treatment of adult patients with newly diagnosed AML who are FLT3 mutation positive as detected by an FDA-approved test and who are eligible to receive standard induction and consolidation chemotherapy. Breakthrough Therapy Designation was supported by improved OS in a phase 3 randomized, double-blind, placebo-controlled trial adding midostaurin or placebo to standard 7+3 induction therapy in adults with newly diagnosed FLT3 mutation positive AML. The 4-year OS was 51.4% in the midostaurin arm compared to 44.2% in the placebo arm, with a median OS of 74.7 months in the midostaurin arm compared to 25.6 months in the placebo arm.

Venetoclex, an oral blc-2 inhibitor, was granted Breakthrough Therapy Designation on 1/25/2016 for use in combination with hypomethylating agents ((b) (4)) for treatment-naïve patients with AML who are ineligible to receive standard induction therapy. (b) (4)

10. Information related to the preliminary clinical evidence:

[3] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design[4], trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

The BTDR is based on the results of Trial CLTR0310-301: A Phase III, Multicenter, Randomized Trial of CPX-351 (Cytarabine:Daunorubicin) Liposome Injection versus Cytarabine and Daunorubicin in Patients 60-75 Years of Age with Untreated High Risk (Secondary) AML. Summaries of the trial design and its results are shown in Tables 3 and 4 below.

Table 3. Protocol CLTR0310-301- Design

Study ID	Phase	Trial Design	Trial Endpoints	Treatment groups
CLTR0310-301	III	Randomized, active-controlled, open-label, multicenter study Population: patients 60-75 years old with t-AML or selected secondary AML*	Primary objective: efficacy -primary efficacy endpoint: OS -secondary efficacy endpoints: overall post-induction response (CR, CR+CRi) rate, best response rate, RFS, EFS -exploratory endpoints: rate of morphologic leukemia-free state, rate of transfer for SCT, and safety	**Arm A/Treatment arm: CPX-351 (n=153)** Induction #1: CPX-351 100 units/m^2 IV, days 1,3,5 Induction #2 (if necessary): 100 units/m^2 IV days 1,3 Consolidation: 65 units/m^2 IV on days 1, 2 (1-2 cycles) **Arm B/Control arm: 7+3 (n=156)** Induction #1: cytarabine 100mg/m^2/day x 7 days, continuously + daunorubicin 60 mg/m^2/day on days 1,2 3 Induction #2: (if necessary): 5+2 (cytarabine 100mg/m^2/day x 5 days + daunorubicin 60mg/m^2 on days 1,2) Consolidation: 5+2 (1-2 cycles)

OS=overall survival, CR=complete remission, CRi=complete remission with incomplete hematologic recovery, RFS=relapse-free survival, EFS=event-free survival, SCT=stem cell transplant

*Secondary AML defined as: bone marrow documention of MDS or CMMoL prior to diagnosis of AML ($_{MDS}$AML, $_{CMMoL}$AML), or AML with FISH or cytogenetic changes linked to MDS per WHO criteria per Swerdlow and Harris, 2008.

Table 4. Protocol CLTR0310-301- Results

	Arm A –CPX-351 N=153	Arm B- 7+3 N=156	HR/OR	p-value (stratified log-rank)
Results in the ITT Population				
OS , median, mo (95% CI)	9.56 (6.6, 11.86)	5.95 (4.99, 7.75)	HR 0.69	0.005
CR Rate, n (%; 95% CI)	57 (37.3%; 29.6,45.4)	40 (25.6%; 19,33.2)	OR 1.69	0.04
By Diagnosis				
t-AML Median OS (mos) (95% CI)	(N=30) 12.17 (7.43, NE)	(N=33) 5.95 (2.92, 8.48)	HR 0.48	
AML-MRC Median OS (mos) (95% CI)	(N=123) 9.07 (5.65,11.33)	(N=123) 5.95 (4.63, 7.79)	HR 0.76	

b. Include any additional relevant information. Consider the following in your response:

[4] Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

- *Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness .*

CLTR0310-301 was a randomized trial comparing CPX-351 to the current standard treatment for patients with treatment-naïve AML with poor prognosis, specifically t-AML and AML-MRC. The primary endpoint was OS, and the study was largely mature. As displayed in Table 4 above, the results of the study showed an OS benefit for the patients treated with CPX-351. The results were supported by the higher CR rate in the CPX-351 arm, and the responses were durable (median duration of remission for the CPX-351 arm 6.93 months (95% CI: 4.6, 9.23) vs 6.11 months (3.45, 8.71) for the control arm). The subgroup analyses showed a consistent treatment effect. Since this was a randomized trial compared to standard available therapy, the above results demonstrate a substantial improvement over such therapy.

- *Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.*

None.

- *Safety data: Provide a brief explanation of the drug's safety profile, elaborating if it affects the Division's recommendation.*

Of the 309 patients enrolled in trial CLTR0310-301, in addition to improved OS in the CPX-351 arm, patients in this arm had a lower rate of early mortality (13.7% compared with 21.2%) than patients in the control arm. As early mortality is a substantial concern for patients treated for AML, especially patients who are older and may be less likely tolerate intensive therapies, this safety benefit should be taken into count in assessing the results attained with CPX-351 as well.

All patients experienced at least 1 AE. Four patients (2.6%) in the treatment arm and 2 (1.3%) in the control arm experienced an AE that led to treatment discontinuation. There was a slightly higher rate of SAEs in the treatment arm (59%, 90/153) than in the control arm (43% , 65/151 patients), but Grade 3-4 AEs occurred at similar rates of 92% in the treatment arm and 91% in the control arm. There was no difference between the arms in the percentage of AEs that led to death (20%, 31/153 in the treatment arm vs 19%, 29/151 in the control arm). Rates of AEs in various categories were similar between the arms, including infection (93% in each arm), febrile neutropenia (68% vs 71%) and sepsis (9.2% vs 7.3%). There was a higher incidence of epistaxis in the treatment arm (36%) as compared to the control arm (18%), as well as blurred vision (6.5% vs 1.3%), cough (33% vs 22%), pneumonia (20% vs 15%), bacteremia (9.8% vs 2%), oraphyngeal pain (18% vs 11%), rash (29% vs 22%) and pruritis (15% vs 8.6%). The Sponsor attributes many of these to more prolonged myelosuppression in the treatment arm.

Overall, the safety profile is not significantly different from that of standard therapy, and the lower rate of early mortality represents an especially clear advantage over combination therapy.

11. Division's recommendation and rationale (pre-MPC review):

☒ GRANT :

Provide brief summary of rationale for granting:

t-AML and AML-MRC are serious conditions which many drug developers have abandoned as untreatable. CPX-351 treatment led to a significant increase in overall survival when compared to treatment with standard AML therapy, and did not add significant toxicity to the standard regimens.

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

☐ DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

12. Division's next steps and sponsor's plan for future development:

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

The Sponsor has a pre-NDA meeting scheduled with the Agency for May 16, 2016. They plan to submit the results of CLTR0310-301 above in support of an NDA for the AML indication by August 31, 2016.

CPX-351 was granted orphan designation for the treatment of AML on 8/22/2008. Pediatric patients may develop t-AML or AML-MRC. We will actively encourage the sponsor to explore dosing, PK, safety and efficacy in pediatric patients with AML.

b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

13. List references, if any:

Dombret H and Gardin C (2016). An update of current treatments for adult acute myeloid leukemia. *Blood,* 127(1):53-61.

Granfeldt Ostgard LS, et al (2015). Epidemiology and Clinical Significance of Secondary and Therapy-Related Acute Myeloid Leukemia: A National Population-Based Cohort Study. *J Clin Oncol* 33:3641-3649.

Hulegardh E, et al. (2015). Characterization and prognostic features of secondary acute myeloid leukemia in a population-based setting: A report from the Swedish Acute Leukemia Registry. *American Journal of Hematology, 90*(3), 208-214.

Harasym T, et al (2010). Drug ratio-dependent antagonism: a new category of multidrug resistance and strategies for its circumvention. In Z. J (Ed.), *Multi-drug Resistance in Cancer-Methods in Molecular Biology* (Vol. 596, pp. 291-323). Springer Science.

Leith CP, et al (1997). Acute myeloid leukemia in the elderly: assessment of multidrug resistance (MDR1) and cytogenetics distinguishes biologic subgroups with remarkably distinct responses to standard chemotherapy. A Southwest Oncology Group study. *Blood, 89*(9), 3323-3329.

Lowenberg B, et al (2009). High-Dose Daunorubicin in Older Patients with Acute Myeloid Leukemia. *New England Journal of Medicine, 361*(13), 1235-1248.

Mayer LD, et al (2006). Ratiometric dosing of anticancer drug combinations: controlling drug ratios after systemic administration regulates therapeutic activity in tumor-bearing mice. *Mol Cancer Ther*, 5:1854-1863.

Schetelig J, et al. (2015). Hematopoietic cell transplantation in patients with intermediate and high risk AML: results from the randomized Study Alliance Leukemia (SAL) AML 2003 trial . *Leukemia, 29*, 1060-1068.

Thein MS, et al (2013). Outcome of Older Patients with Acute Myeloid Leukemia: An Analysis of SEER Data over Three Decades. *Cancer*, 119 (15).

14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

15. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation	☒
Deny Breakthrough Therapy Designation	☐

Reviewer Signature:	{See appended electronic signature page}
Team Leader Signature:	{See appended electronic signature page}
Division Director Signature:	{See appended electronic signature page}

5-7-15/M. Raggio

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

/s/

AVIVA C KRAUSS
05/09/2016

DONNA PRZEPIORKA
05/09/2016

ANN T FARRELL
05/09/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 72939

MEETING MINUTES

Celator Pharmaceuticals
Attention: Donna Cabral-Lilly, Ph.D.
Head of Pharmaceutical Development
303B College Road East
Princeton, NJ 08540

Dear Dr. Cabral-Lilly:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CPX-751.

We also refer to the meeting between representatives of your firm and the FDA on Wednesday, May 25, 2011. The purpose of the meeting was to discuss clinical development after phase 2 trials.

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

If you have any questions, call me, at (301) 796-2848.

Sincerely,

{See appended electronic signature page}

Theresa Ferrara, MPH
Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: May 25, 2011 3:00 – 4:00pm
Meeting Location: White Oak Building 22, Room 1311

Application Number: IND 72939
Product Name: CPX-351
Indication: acute mylogenous leukemia
Sponsor/Applicant Name: Celator Pharmaceuticals

Meeting Chair: Qin Ryan, MD, PhD
Meeting Recorder: Theresa Ferrara, MPH

FDA ATTENDEES

Ann Farrell, MD, Acting Director, Division of Hematology Products
Ed Kaminskas, MD, Acting Deputy Director, Division of Hematology Products
Qin Ryan, MD, PhD, Acting Clinical Team Leader, Division of Hematology Products
Ashkan Emadi, MD, PhD, Clinical Reviewer, Division of Hematology Products
Mark Rothmann, PhD, Biometrics Team Leader
Kallappa Koti, PhD, Biometrics Reviewer
Bahru Habtemariam, PhD, Clinical Pharmacology Reviewer
Theresa Ferrara, MPH, Regulatory Project Manager

SPONSOR ATTENDEES

Arthur Louie, MD, Chief Medical Officer
William Hahne, MD, VP, Clinical Research
Donna Cabral-Lilly, PhD, Head of Pharmaceutical Development
Lawrence Mayer, PhD, President and Head of Research
Kim Paulsen, Manager, Clinical Operations

Consultants:

(b) (4)

1.0 BACKGROUND

On February 14, 2006, Celator submitted an IND (072939) for a Phase I trial related to CPX-351. CPX-351 liposome injection is a fixed 5:1 molar ratio of cytarabine and daunorubicin encapsulated within a liposome. The Phase I trial completed accrual in November 2008 with results submitted to the IND on June 01, 2010.

There are currently two randomized Phase II trials with CPX-351 for the treatment of acute myelogenous leukemia (AML). The first Phase II trial compares CPX -351 versus the "7+3" regimen of cytarabine and daunorubicin in patients 60-75 years of age with newly diagnosed AML. This study completed enrollment in October 2009 and treated 126 patients of 127 randomized. Data from the first year of this study are available. Study follow up has been extended to two years, as the median survival had been reached in only the CPX-351 arm of the study at one year. The second Phase II trial compares CPX-351 versus intensive first salvage therapy in patients 18-65 years of age with AML in first relapse. Enrollment was completed in November 2010 after 126 patients were registered and treated. Data from this study are pending.

The sponsor submitted a briefing book to the FDA with a brief summary of the clinical information on CPX-351 that has been collected to date.

In addition, the sponsor provided a draft of the Phase III trial, which is intended for registration. The sponsor also provided specific questions (below) about the protocol design and analysis to be discussed at the May 25, 2011 meeting with the Agency.

2.0 DISCUSSION

1. Patient Population

Secondary AML is a subset of AML patients meeting WHO AML criteria with a history of prior chemotherapy (treatment related AML, t-AML), or AML arising from an antecedent hematologic disorder (AHD) such as myelodysplasia (MDS), myeloproliferative neoplasm (MPN), combined myelodysplasia and myeloproliferative disease (MDS/MPN), or chronic myelomonocytic leukemia (CMMoL). This is an important subgroup of AML patients with poor prognosis. It may constitute as many as 10-30% of all AML patients and is characterized by poorer response rates, shorter duration of remission, and shorter overall survival when compared to *de novo* patients.[10]

Celator proposes to treat secondary AML patients with t-AML, AML with myelodysplasia-related changes and AML with a history of CMMoL as defined by the World Health Organization. The diagnoses are based on objective criteria and stratification using age and cytogenetic status reliably identifies high risk patients. In Study 204 these sub-groups constituted 82% of the secondary AML patients (42/51 patients). Celator was advised by its Clinical Advisory Board to exclude patients with MPN and combined MDS/MPN because patients with these subtypes of secondary AML have highly variable prognosis and because their inclusion would introduce an additional layer of complexity in stratifying patients as well as interpreting the data.

In summary, patients age 60-75 with MDS and CMMoL who have transformed to AML and treatment-related AML patients will be randomized 1:1 to receive either CPX-351 or 7+3 chemotherapy. The diagnosis will be confirmed by a review of history and bone marrow data by an independent pathologist.

Question 1: Does FDA agree that this subgroup of secondary AML is a suitable population for a labeled treatment indication?

FDA Response to Question 1:
We understand you to mean that this subgroup consists of patients with t-AML, AML with myelodysplasia-related changes and AML with a history of CMMoL as defined by the World Health Organization. This selection appears to be acceptable.

2. Stratification

Historically, the secondary AML population is known to have poor prognosis after transformation to AML with high rates of early death, low rates of CR, early relapse after achievement of CR, and poor survival after first-line treatment. Patients will be stratified on the basis of their cytogenetics (adverse vs. non-adverse) and age at randomization (60-69 vs. 70-75). Patients with adverse cytogenetics or age ≥70 are expected to have worse prognosis and will be stratified to the high risk group. All other patients with non-adverse cytogenetics and age 60-69 will be stratified to the standard risk group.

Question 2: Does FDA agree that these are reasonable criteria for stratification?

FDA Response to Question 2:
Please explain your terminology of non-adverse and adverse cytogenetics. Please provide your rationale for stratification based on age (60-69 vs. 70-75).

3. Primary Efficacy Endpoint and Sample Size

Study 204 demonstrated that the subgroup of secondary AML patients had the most consistent "signal" for efficacy when CPX-351 was compared against 7+3 induction treatment. This signal was marked by:

- Improvement in overall survival (HR=0.41; p=0.01)
- Potential improvement in event free survival (HR=0.56; p=0.07),
- Potential improvement in CR+CRi rate (18/32 (56.3%) vs. 6/19 (31.6%); p=0.15).

Celator proposes to use overall survival as the primary efficacy endpoint with analysis using the logrank test.

Celator is aware of the risk that an observed difference in efficacy from a small Phase II study might over-predict for efficacy in a subsequent larger trial. Consequently, we chose to increase the power of the proposed Phase III study in order to detect a smaller efficacy difference than was observed in the Phase II study. The proposed sample size was calculated and is reflected in the sample size table (Table 2) shown below which provides guidelines for sample sizes to cover different anticipated hazard ratios.

Table 1: Sample Size Calculations

Median Survival	12 months f/u		18 months f/u		24 months f/u	
	Years of Accrual	Total Sample Size	Years of Accrual	Total Sample Size	Years of Accrual	Total Sample Size
6 Months						
HR=0.55 (1.82)	1	154	1	138	0.9	130
HR=0.60 (1.67)	1.4	200	1.2	182	1.2	180
HR=0.65 (1.54)	1.75	266	1.65	248	1.65	238
HR=0.70 (1.43)	2.5	368	2.45	350	2.25	342
7 Months						
HR=0.55 (1.82)	1.1	166	1	150	1	140
HR=0.60 (1.67)	1.4	210	1.3	190	1.2	180
HR=0.65 (1.54)	1.85	278	1.7	258	1.6	246
HR=0.70 (1.43)	2.55	382	2.5	360	2.4	348

Assumes a one-sided α=0.025, power=90% and an accrual rate of approximately 150 patients/year.

Celator proposes to use a sample size of (b)(4) evaluable secondary AML patients per arm allowing detection of a hazard ratio of (b)(4) with (b)(4)% power. In discussions with senior hematology advisors there was agreement that a hazard ratio of (b)(4) in an overall survival analysis, if achieved, would reflect a clinically meaningful difference in this patient population.

Based on previous discussions with FDA and given the randomized design and overall survival primary endpoint with standard logrank analysis, Celator believes that this sample size will be adequate for a demonstration of efficacy in a single pivotal study.

Question 3: Does FDA agree that given the randomized design and overall survival primary endpoint with standard logrank analysis, the proposed sample size will be adequate for a demonstration of efficacy in a single pivotal study suitable for registration?

FDA Response to Question 3:
A randomized design with overall survival as the primary endpoint could be acceptable. However, your drug development plan and proposed statistical analysis plan are problematic. With one trial you are attempting to demonstrate that your agent can be used for induction and consolidation. Additionally in the same trial you do not deal with the issue of transplant as there is no randomization for transplant. Thus an imbalance could occur as a result of using transplant in favor of your agent or in favor of the control. Additionally your decision rule for second induction is not clear and could confound the interpretation of the efficacy and safety results.

Additionally we are concerned with your proposed treatment regimens particularly for the control arm. See response to question 4.

Please note that a non-ITT analysis would not be acceptable for approval nor a labeling claim.

Meeting Discussion:
The FDA shared concern with the sponsor regarding the potential imbalance between the two arms that could occur. The sponsor plans to address this concern with increasing sample size, protocol revisions, and company internal meetings. The sponsor proposes to do a sensitivity analysis. The sponsor agrees to clearly clarify eligibility criteria for reinduction therapy.

4. Secondary Efficacy Endpoints

Response Assessment Criteria

During the Treatment Phase patients will be assessed for response according to the following criteria:

Complete remission (CR)[1]	Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count >1.0 x 10^9/L (1000/μL); platelet count >100 x 10^9/L (100,000/μL); independence from red cell transfusions
CR with incomplete recovery (CRi)[2]	All CR criteria except for residual neutropenia (<1.0 x 10^9/L [1000/μL]) **and/or** thrombocytopenia (<100 x 10^9/L [100,000/μL])
Treatment failure	
Persistent Disease (PD)	Failure to achieve CR or CRi; only includes patients surviving ≥7

	days following completion of initial treatment, with evidence of persistent leukemia by blood and/or bone marrow examination
Death in aplasia	Deaths occurring ≥7 days following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia
Death from indeterminate cause	Deaths occurring before completion of therapy, or <7 days following its completion; or deaths occurring ≥7 days following completion of initial therapy with no blasts in the blood, but no bone marrow examination available
Relapse[3]	Bone marrow blasts ≥5%; or reappearance of blasts in the blood after achievement of a CR or CRi; or development of extramedullary disease

[1]All criteria need to be fulfilled; marrow evaluation should be based on a count of 200 nucleated cells in an aspirate with spicules; if ambiguous, consider repeat exam after 5 to 7 days; flow cytometric evaluation may help to distinguish between persistent leukemia and regenerating normal marrow; a marrow biopsy should be performed in cases of dry tap, or if no spicules are obtained; no minimum duration of response required.
[2] Some patients may not achieve complete hematologic recovery upon initiation of consolidation.
[3]In cases with low blast percentages (5-10%), a repeat marrow should be performed to confirm relapse. Appearance of new dysplastic changes should be closely monitored for emerging relapse. In a patient who has been recently treated, dysplasia or a transient increase in blasts may reflect a chemotherapy effect and recovery of hematopoiesis.

The response of patients with no post-baseline bone marrow assessment is entered as not done.

Timing of response assessment

The patient's response to induction therapy will be assessed on the first day when all criteria for CR are met. The bone marrow assessment and the peripheral counts will not be required to be performed on the same day, but recovery of counts (including absence of peripheral blasts) must be performed within 14 days of the bone marrow assessment. The timing of other outcomes is recorded as follows:

- After one or two induction course(s), PD is declared on the day of the bone marrow showing persistent AML
- After one or two inductions induce aplasia, PD is declared on the day of the bone marrow showing persistent disease in a recovering marrow.
- CRi is declared on or after Day 56 when the patient's bone marrow (performed between Day 42-56) demonstrates absence of leukemia and the peripheral blood counts have partially recovered but appear stable (performed at least twice between Day 42-56) and no further induction therapy is planned.
- For patients with sufficient blood count recovery that consolidation therapy is planned, CRi is declared on the day consolidation therapy is initiated but the peripheral counts have not met the full CR criteria. Consolidation must begin after Day 42.

CR+CRi Rate and Duration

Celator proposes that response rate (CR+CRi) and response duration be used as secondary endpoints. CR and CRi provide a direct indication of the ability of induction therapy to clear the bone marrow of leukemia. While a relative improvement in CR+CRi rate alone may not be sufficient as an indicator of overall clinical benefit, response rate coupled with an acceptable comparative response duration in a randomized trial may be.

Best Response

Patients who complete induction(s) therapy with a response of CRi may be upgraded to a CR if the patient's peripheral blood counts meet criteria for CR (absolute neutrophil count of >1000/μL and platelet count of >100,000/μL) after declaration of a CRi. A repeat bone marrow assessment will be made if greater than 60 days have elapsed since the last assessment in order to complete documentation of best response of CR. This will be helpful in CRi patients who complete consolidation treatment and recover neutrophil and platelet counts in follow-up.

Event-free Survival

Event-free survival (EFS) will be a secondary endpoint assessed in all randomized patients. Event-free Survival is defined as the time from study randomization to the date of induction treatment failure (persistent disease), relapse from CR or CRi, initiation of non-protocol chemotherapy (e.g. salvage therapy) or death from any cause, whichever comes first. Patients transferred to transplant will be censored for Event-free Survival at the start of conditioning therapy. Patients alive and not known to have any of these events are censored on the date they were last examined. By tracking time to documentation of persistent leukemia after induction, time to relapse after CR, and time to death, EFS provides a sensitive measure of both efficacy and safety that can be directly attributed to study treatment. Celator believes that EFS provides supportive evidence of efficacy.

(b) (4)

Question 4: Does FDA agree with the use of CR+CRi rate, CR+CRi duration, Best Response, Event-free Survival, (b) (4) as secondary endpoints supplementing the primary endpoint of overall survival and with their definitions?

FDA Response to Question 4:

- **You should note that in the absence of clinically meaningful overall survival benefit, none of your secondary endpoints will be considered for any indication claim or inclusion in labeling.**
- **You should standardize how you will evaluate blast counts in the bone marrow or peripheral blood.**
- **Furthermore, the validity and usefulness of CRi is not established; we discourage you of using CRi as the endpoint.**
- **Event free survival and (b) (4) are not acceptable as endpoints.**
- **Please discuss and clarify the eligibility for reinduction therapy.**
- **Your proposed consolidation regimen for the control arm is not acceptable. This regimen is not safe and is not used as standard practice.**

- **Transplant could confound study results making it impossible to isolate the effect of your agent. Please discuss strategies to ensure this possibility does not happen. You may wish to enroll only patients eligible for transplant.**
- **Please discuss the types of transplant you anticipate patients enrolled will receive.**
- **Please explain how you plan to evaluate and isolate the treatment effect of your agent recognizing the potential effect of stem cell transplant on overall survival.**
- **We recommend that Cochran-Mantel-Haenzsel test be used for comparing response rates between treatments.**
- **The duration of CR+CRi rate should be summarized and not statistically compared.**
- **In the absence of a statistically significant result for the primary analysis of the primary endpoint, results based on secondary endpoints or subgroups can not result in (either singly or in combination) an efficacy claim. In the event that there is a statistically significant result for the primary analysis of the primary endpoint, and FDA determines that flaws in the design and/or modifications in the study over time do not confound the reliability and confidence in the results, those secondary endpoints that are significant after proper adjustment for multiplicity may be included in the label. Please include in a future submission any secondary endpoints for which claims may be included in the labeling. Please explain how adjustments will be made for multiplicity to guarantee an overall 2-sided 0.05 level for the tests of such secondary endpoints.**

Meeting Discussion:
The sponsor agreed to change the consolidation regimen for the control arm.
FDA stated that event-free survival and relapse-free survival are exploratory and will not be considered for labeling.

5. Hematopathology Review

Because AML is almost always a rapidly progressive disease, the diagnosis, once made, propels treating physicians to start therapy as soon as possible. As a consequence, independent review of diagnosis with confirmation of secondary AML in most cases will not occur before the initiation of treatment. It is expected that post hoc independent review of history and bone marrow findings will be adequate as confirmation in a randomized setting. Thus, the analysis of efficacy will be performed on an intent-to-treat basis with diagnosis established locally. The independent confirmation of diagnosis will be used to define a per-protocol eligible subgroup which will also be analyzed for concordance. Every attempt will be made at the time of randomization to collect sufficient information to maximize the probability that each patient is in fact eligible for the protocol.

The definition of MDS and CMMoL will be according to WHO criteria. For patients with a history of MDS or CMMoL, every attempt will be made to obtain the records confirming the diagnosis. If there is doubt about the diagnosis of MDS or CMMoL during the process of independent review, slides will be requested and reviewed. The majority of patients with MDS or CMMoL will already have been assessed for cytogenetic abnormalities as part of their work up and these records will also be requested. At diagnosis of AML, all patients will be required to have bone marrow evidence of AML and a new evaluation of cytogenetics will be performed looking for advancing cytogenetic changes. For some patients, the diagnosis of MDS or CMMoL will require cytogenetic evidence and/or evidence of dysplasia obtained from the screening bone marrow.

Patients with t-AML will have a detailed history obtained documenting their history of prior malignancy and its treatment. If possible, prior medical records will be obtained documenting the extent of exposure

with prior chemotherapy. The specific prior chemotherapies defining t-AML will be according to WHO criteria.

Celator believes that this is a reasonable approach in a randomized setting with Overall Survival as the primary endpoint.

Question 5: Does FDA agree that this process for confirmation of diagnosis in a randomized setting with Overall Survival as the primary endpoint is suitable for a registration study?

FDA Response to Question 5:
No. To avoid any potential bias, you should document all eligibility criteria locally before randomization.
Please provide a clear clarification with respect to the use of hydroxyurea or other cytoreductive agents including dose and duration.

Please note that a non-ITT analysis would not be acceptable for approval nor a labeling claim.

Meeting Discussion:
FDA and the sponsor had wide range of discussion regarding the responses to question 5. The sponsor understands the Agency's concerns and will incorporate them into the protocol.

6. DSMB

The proposed randomized study will be supported by a DSMB, which will be given the responsibility of ongoing monitoring of safety (e.g. review of SAE data). The DSMB will consist of two senior hematologists, one cardiologist, and one statistician. This group will be empowered to review study data compiled by independent vendors without direct supervision from Celator. The scope of activities and frequency of review will be specified in a charter. The DSMB will make recommendations to the sponsor, if necessary, for changes in the conduct of the study. A single assessment of 60-day mortality will be made with early stopping rules, established by the DSMB.

Question 6: Does the FDA agree with the DSMB objective of assessing safety and early stopping rules via the 60-day mortality assessment?

FDA Response to Question 6:
Please describe in further detail the early stopping rule via the 60-day mortality.

The interim analysis for futility should not be used to alter the design and conduct of the trial.

7. Adequacy of the total database for obtaining registration

Celator proposes to submit for registration, data from this proposed pivotal Phase III study along with supporting data from the randomized Phase II studies conducted in newly diagnosed elderly patients with AML and first relapse AML. Celator believes that the combined data from the three studies will provide substantial evidence of the efficacy and safety of CPX-351 and will be sufficient for filing for marketing approval for sAML.

At the completion of this Phase III trial, the safety database will consist of the following:

Table 2: Approximate Safety Database at time of NDA filing

	Patients	
Study	**CPX-351**	**Control**
301 (Phase III)	77	77 (7+3)
204 (Phase II)	85	41 (7+3)
205 (Phase II)	81	45 (salvage)
206 (QT/QTC Phase II)	24	
101 (Phase I)		
At MTD	20	
At other doses	28	
Safety Database at MTD	**287**	
Total Safety Database all dose levels	**315**	

Table 3: Approximate Efficacy Database: First-line treatment, secondary AML only

	Patients	
Study	**CPX-351**	**7+3**
301 (Phase III)	77	77
		(b) (4)

Celator believes that the safety and efficacy databases will be sufficient for obtaining registration.

Question 7: Does FDA agree that the safety and efficacy databases will be sufficient for obtaining registration?

FDA Response to Question 7:
Your safety database appears to be acceptable. However, it will be a review issue.

You should not pool data from phase II and phase III trials for efficacy analyses or claims.

8. Adequacy of Pharmacology Specimen Collection within the Phase III Study

After consultation with FDA in January 2011, Celator agreed to obtain additional pharmacology information in the Phase III study with regards to assessment of variability in the handling of CPX-351-derived cytarabine, daunorubicin, and copper in the population of treated patients prior to NDA submission. The Phase III protocol proposes to collect 4 samples from each patient randomized to CPX-351 in the 96 hours after Day 5 treatment. CPX-351 patients will be sub-randomized to one of two PK sampling schedules. Schedule 1: Day 1: 45 min, 3 hrs, 8 hrs, prior to dosing on Day 3 (48 hrs (+/- 6 hrs)) or Schedule 2: Day 1: End of Infusion, 2 hrs, 6 hrs, prior to dosing on Day 5 (96 hr (+/- 6 hrs)). Each sample will be assayed for total cytarabine, daunorubicin, Ara-U, and daunorubicinol. In addition, all

patients in both the CPX-351 and the 7+3 arms of the study will be assessed for serum copper levels until those levels return to baseline.

Question 8: Celator believes that the Clinical Pharmacology specimen collections proposed for the Phase III study are consistent with the suggestions made by FDA at the January 2011 meeting and are acceptable. Does FDA agree?

FDA Response to Question 8:
1). In order to perform informative exposure-response analysis for safety and effectiveness, you should obtain additional PK samples from all ARM A patients on day 7.
2) The current copper level sampling plan will not allow detection of peak serum copper levels. Your preclinical study in rat showed that peak copper levels occur 1 day after CPX-351 administration. Therefore, at minimum, you should collect additional serum copper levels on days when CPX-351 PK samples are collected (on days 1, 3, 5, and 7).

Meeting Discussion:
Sponsor agreed with point # 1 above. Sponsor agreed to collect copper samples at peak (day 5 or 7) and consider an intermediate timepoint.

3.0 OTHER IMPORTANT MEETING LANGUAGE SECTIONS:

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Celator to provide justification for patient stratification for Phase 3 study	Celator	When Celator has gathered the relevant data

6.0 ATTACHMENTS AND HANDOUTS

No attachments or handouts for the meeting minutes.

Minutes Preparer:

{See appended electronic signature page}

Theresa Ferrara, MPH
Regulatory Project Manager

Meeting Chair:

{See appended electronic signature page}

Qin Ryan, MD, PhD
Clinical Team Leader

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

/s/

THERESA A FERRARA
06/07/2011

QIN C RYAN
06/07/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 072939

MEETING MINUTES

Celator Pharmaceuticals, Inc.
303 B College Road East
Princeton, NJ 08540

Attention: Arthur C. Louie, MD, FACP
Chief Medical Officer

Dear Dr. Louie:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CPX-351.

We also refer to the meeting between representatives of your firm and the FDA on July 29, 2010. The purpose of the meeting was to discuss clinical issues pertinent to the planned conduct of a randomized two arm pivotal clinical trial leading to a potential NDA and registration.

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

If you have any questions, call me at (301) 796-4256.

Sincerely,

{See appended electronic signature page}

Christy Cottrell
Regulatory Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End-of-Phase 2

Meeting Date and Time: July 29, 2010 at 1:00 pm
Meeting Location: WO22, Room 1315

Application Number: IND 072939
Product Name: CPX-351
Indication: [redacted] (b) (4) **acute myelogenous leukemia**
Sponsor/Applicant Name: Celator Pharmaceuticals

Meeting Chair: Edvardas Kaminskas, MD
Meeting Recorder: Christy Cottrell

FDA ATTENDEES

Edvardas Kaminskas, MD, Deputy Director, DHP
Qin Ryan, M.D., PhD, Clinical Team Leader, DHP
Angelo DeClaro, MD, Clinical Reviewer
Mark Rothmann, PhD, Biometrics Team Leader
Kallappa Koti, PhD, Biometrics Reviewer
Bahru Habtemariam, Pharm.D., Clinical Pharmacology Reviewer, DCP5
Christy Cottrell, Regulatory Project Manager

SPONSOR ATTENDEES

Arthur Louie, MD, Chief Medical Officer
William Hahne, MD, VP Clinical Research
Donna Cabral-Lilly PhD, Head of Pharmaceutical Development
Lawrence Mayer, PhD, President and Head of Research
Michael Chiarella, Director Clinical Operations
Martin Tallman, MD, Therapeutic Expert for AML
[redacted] (b) (4) Regulatory Consulting
[redacted] (b) (4) – statistical consultant

BACKGROUND

The sponsor is currently conducting two randomized Phase 2 studies in AML. The first study compares CPX-351 versus the standard "7+3" regimen of cytarabine and daunorubicin in patients 60-75 years of age with newly diagnosed AML. The study has completed enrollment and 126 patients were treated. The second study compares CPX-351 versus intensive first salvage therapy in patients 18-65 years of age with AML in first relapse. The study has enrolled 78 patients of a planned 120 patient population.

The sponsor is proposing a randomized Phase 3 study comparing CPX-351 (100 units/m^2, days (b) (4) to 60 mg/m^2 daunorubicin on days 1, 2, and 3 in combination with 100 mg/m^2 of cytarabine by continuous infusion for 7 days. The patient population would be elderly patients (age 60 and older) with newly diagnosed, untreated AML and the primary endpoint would be (b) (4)

Draft responses were sent to the sponsor on July 28, 2010.

DISCUSSION

1. Celator believes that the background data described above and in Section 10.0 and completion of this development plan should be sufficient to meet FDA's requirements for a fixed-combination prescription drug. **Does FDA agree?**

   FDA RESPONSE: You will need to provide this information plus the original publications (e.g., clinical trials) which outline the development of the combination chemotherapy regimens using cytarabine plus daunorubicin.

   MEETING DISCUSSION: *None.*

2. FDA has requested randomized trials to assess safety and efficacy in appropriately selected elderly patients with AML. Celator believes the appropriate comparator arm for a potential Phase III, two arm randomized pivotal trial to be conducted in elderly AML patients is conventional "7+3" therapy defined as cytarabine 100 mg/m^2/d x 7 days and daunorubicin 60 mg/m^2 on day 1, 2, and 3. This trial would look for superior efficacy compared to control and will be conducted in patients with newly diagnosed AML. **Does FDA agree that this is an appropriate comparator?**

   FDA RESPONSE: Yes. See also response to Question #4.

   MEETING DISCUSSION: *None.*

3. **Does the FDA agree that this patient population is appropriate and sufficiently well-defined?**

   FDA RESPONSE: The proposed patient population appears to be acceptable for your proposed randomized study comparing CPX-351 and standard 7+3. However, the patients who are eligible for HDAC should be excluded from the study.

   We do not understand what you mean by the following on page 40: "It is expected that few patients meeting the objective eligibility criteria… randomization process."

   MEETING DISCUSSION: *The Division clarified that HDAC= high dose Ara-C.*

4. [redacted] (b) (4) **Does FDA agree?**

FDA RESPONSE: No. Overall survival should be the primary efficacy endpoint. You need to demonstrate superiority of CPX-351 compared to "7+3" as measured by overall survival. Please see the Agency's response to Question 16 and the additional comments. No other endpoint or analysis will be considered for efficacy if the primary analysis of OS for the ITT population is negative. If you wish to demonstrate non-inferiority, you will need to conduct two adequate and well-controlled randomized trials.

MEETING DISCUSSION: ***(handout)*** *The sponsor understands the Division's recommendation for OS as the primary efficacy endpoint.* [redacted] (b) (4) *The Division suggested that the sponsor submit their proposal for review. The Division also recommends that the sponsor review the transcripts from the September 2009 ODAC on leukemia study design.*

5. **Does FDA agree that the endpoints as defined are adequate for capturing clinical benefit?**

FDA RESPONSE: No. See response to Question #4.

MEETING DISCUSSION: *None.*

6. **Does the Agency agree that the diagnosis of AML should be made locally and that independent review of reports of screening bone marrow examinations is adequate?**

FDA RESPONSE: This is irrelevant to the primary endpoint of OS. See response to Question #4.

MEETING DISCUSSION: *The sponsor clarified that the diagnosis will be made locally and the patient will be assigned to the treatment arm based on local diagnosis. Confirmation of diagnosis will be made by independent review later (so as not to delay patient treatment). If there is discordance between diagnoses, there will be a mechanism built into the protocol to deal with patient assignment.*

7. **Does the Agency agree** [redacted] (b) (4)

FDA RESPONSE: No.

MEETING DISCUSSION: *None.*

8. **Does the Agency agree** [redacted] (b) (4) **?**

FDA RESPONSE: No, a confirmatory bone marrow examination with cytogenetics will be required. We strongly discourage you from using any endpoints other than OS for primary analysis in your study. No secondary endpoints will be considered if the primary analysis, OS, fails to show a favorable risk benefit ratio. See response to Question # 4.

MEETING DISCUSSION: *The sponsor explained the difficulties with performing a confirmatory bone marrow remission examination (IRBs/insurance will not approve, invasive treatment, not standard practice, not outlined in IWG). The sponsor is planning to do two bone marrows on day 14 and 28 to define CR. This will be further clarified in the SPA submission.*

9. **Does the Agency agree** [redacted] (b) (4) **?**

FDA RESPONSE: No, we do not agre [redacted] (b) (4) Also, see response to Question # 4.

MEETING DISCUSSION: *The sponsor clarified that the definition of remission is made solely on morphology. This will be further clarified in the SPA submission.*

10. **Does the Agency agree that additional bone marrow examinations are not required during the period of consolidation treatment but that after consolidation, regularly scheduled bone marrow examinations every 3-4 months for two years and every 6 months thereafter will be adequate?**

FDA RESPONSE: Yes, beyond the confirmatory bone marrow examination with cytogenetics additional confirmatory bone marrow examinations are not required in addition to the schedule mentioned above.

MEETING DISCUSSION: *None.*

11. **Is the described approach for establishing a DSMB for the Phase III study acceptable to the agency?**

    FDA RESPONSE: It is acceptable.

    MEETING DISCUSSION: *None.*

12. Celator proposes that data from [redacted] (b) (4) and the proposed Phase III randomized study to be submitted for a SPA will be adequate for registration. **Does FDA agree?**

    FDA RESPONSE: No. Proposed type I error rate of [redacted] (b) (4) is not acceptable for a registration study. [redacted] (b) (4) Please see the Agency's response to Question 16 and the additional comments.

    In general, the adequacy of studies to support a regulatory submission will be a review issue at the time of NDA action. See above.

    MEETING DISCUSSION: *The Division typically recommends two randomized, controlled trials (RCT), however, acknowledges that one well-designed and well-conducted Phase 3 RCT with a supportive Phase 2 study may be sufficient provided that the results of the Phase 3 study would be sufficiently convincing and statistically persuasive so that a second study would not be ethical or possible to perform.*

13. **Does FDA agree that modification of the 205 study is acceptable?**

    FDA RESPONSE: No. The proposed study population does not meet the definition of unmet medical need as described in the accelerated approval regulations (Subpart H). The 205 study could be utilized as a supportive study in a NDA submission of your Phase 3 study.

    MEETING DISCUSSION: *The Division referred the sponsor to the September 2009 ODAC meeting. Ultimately, unmet medical need and accelerated approval is a review issue.*

14. **Does FDA agree that, depending on results ([redacted] (b) (4)), this study would have the potential to support accelerated approval?**

    FDA RESPONSE: No. See response to Question #13.

    MEETING DISCUSSION: *None.*

15. **Does FDA agree that no statistical penalty should be paid for this modification since the proposal for modification is based only on data from outside of the 205 study?**

    FDA RESPONSE: Yes.

    MEETING DISCUSSION: *None.*

16. **Does FDA agree that the use of an adaptive designed Phase III trial would be a potentially acceptable design for registration?**

    FDA RESPONSE: No. We have concerns regarding your proposed Phase 3 study design.

    We recommend that the Phase 3 study should be a full fledged study- (b) (4) We recommend that overall survival be the primary endpoint and that you analyze the overall survival data using a stratified log-rank test to demonstrate superiority of CPX-351 over "7+3". In addition, please be advised that frequent interim analyses raise critical concerns regarding un-blinding. We discourage multiple interim analyses (b) (4) . We recommend that you use the group sequential method for OS data analysis. Also see the additional comments.

    MEETING DISCUSSION: *The sponsor proposes overall survival as the primary endpoint, with one analysis at the end of study (log-rank) and Bayesian predictive calculations to decide when to stop accrual. An interim analysis would be performed for futility and efficacy. The sponsor will submit a proposal with the SPA submission.*

ADDITIONAL COMMENTS

1. **Feedback from QT-IRT on cardiac monitoring plans: Celator plans to specifically address the cardiac safety of CPX-351 because daunorubicin, an anthracycline and component of this product, is a known cardiotoxic agent. As part of this evaluation a cohort of patients treated at the recommended dose will be evaluated according to guidelines established in ICH E14. Is this approach acceptable?**

   FDA RESPONSE: In general, conducting an ECG sub-study in an adequate number of subjects to exclude large ECG effects at the maximum proposed therapeutic dose or maximum tolerated dose is acceptable. Please submit the ECG sub-study protocol for review prior to study conduct.

2. Explain the apparent discrepancy in dosing on page 7 where you state that patients will receive CPX-351 on Days 1, 3, and 5 and on page 11 where you state that patients will receive CPX-351 on Days (b) (4)

3. Explain the difference between consolidation and reinduction as you have outlined on page 21.

4. Explain what is meant by the last sentence on page 21: "In addition, Celator proposes (b) (4) .

5. Clarify if the European prognostic index is the stratification factor in the Phase 3 study as well.

6. Provide details on the randomization procedure in the proposed Phase 3 "adaptive" study.

7. You need to identify and define the primary analysis patient population in the statistical analysis plan.

8. On page 1 of Appendix 3, you have stated: "A p-value of less than (b) (4)% for the test of proportions enables a claim of superiority. The value of (b) (4)% is chosen to ensure the overall Type I error rate is less than 2.5%." Please clarify if (b) (4)% is a typographical error. A similar discrepancy appears on page 3 of Appendix 3.

9. What is the test procedure that is used at the time of the definitive analysis of ORR.

10. Proposed type I error rate of (b) (4) is not acceptable for a registration study. Additionally, in section 10.7 (p. 41 of Volume 1; Appendix 2), you have proposed Fisher's exact test for comparing the proportion of patients surviving at 1 year between treatments. Please explain how will the loss to follow-up prior to one (or two) year be handled in the analysis.

11. As communicated previously on 4/29/2010, we remind you to submit your clinical pharmacology development plan for agency review and concurrence.

MEETING DISCUSSION: *None.*

ISSUES REQUIRING FURTHER DISCUSSION
None

ACTION ITEMS
None

ATTACHMENTS AND HANDOUTS
Attached

_____	Concurrence:	_____
Christy Cottrell		Edvardas Kaminskas, MD
Regulatory Project Manager		Deputy Director, DHP
Minutes Recorder		Meeting Chair

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-72939	GI-1	CELATOR PHARMACEUTICALS INC	CPX-351 LIPOSOME INJECTION

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

/s/

CHRISTY L COTTRELL
09/14/2010

EDVARDAS KAMINSKAS
09/15/2010