CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209401Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 209401
Addendum to Review #1

Drug Name/Dosage Form	VYXEOS (Cytarabine and Daunorubicin) Liposome Injection/Lyophilized liposome dispersion
Strength	44 mg daunorubicin and 100 mg cytarabine
Route of Administration	Injection
Rx/OTC Dispensed	Rx
Applicant	Celator Pharmaceuticals, Inc. (a Jazz Pharmaceuticals company)
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
0002	*March 31, 2017*	*CMC*
0003	*April 26, 2017*	*Drug Product*
0009	*May 10, 2017*	*Facility, Drug Product*
0012	*May 19, 2017*	*CMC*
0013	*May 24, 2017*	*Drug Product, Process*
0017	*May 30, 2017*	*Biopharm*
0019	*June 02, 2017*	*Microbiology, Drug Product*
0021	*June 07, 2017*	*Drug Product, Process*
0026	*June 15, 2017*	*Microbiology, Drug Product, ,Biopharm*
0029	*June 20, 2017*	*Drug Product*
0030	*June 20, 2017*	*Labeling*
0035	*June 30, 2017*	*Drug Product, Process*
0036	*July 10, 2017*	*Drug Product*
0037	*July 13, 2017*	*Labeling*
0038	*July 13, 2017*	*Drug Product, Process*
0040	*July 18, 2017*	*Process*
0041	*July 18, 2017*	*Drug Product*
0045	*July 21, 2017*	*Drug Product*
0048	*July 27, 2017*	*Labeling*
0050	*July 31, 2017*	*Labeling*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Monica Cooper Charles Jewell	Ben Stevens
Drug Product	Paresma Patel	Anamitro Banerjee
Process	Kumar Janoria	Edwin Jhao
Microbiology	David Bateman	Jessica Chiaruttini
Facility	Christina Capacci-Daniel	Derek Smith
Biopharmaceutics	Gerlie Gieser	Okponanabofa Eradiri
Regulatory Business Process Manager	Teshara Bouie	NA
Application Technical Lead	Anamitro Banerjee	NA
Laboratory (OTR)	Michael Hadwiger	
ORA Lead	Dennis Cantellops	
Environmental	NA	

Executive Summary

I. Recommendations and Conclusion on Approvability

The NDA209401 is recommended for APPROVAL from the CMC point of view. The quality information provided in this NDA is acceptable

Action letter language (to be communicated to the applicant):
An expiration dating period of 48 months is granted for this product when stored at 2 ℃ to 8 ℃ (36 ℉ to 46 ℉) protected from light.

II. Summary of Quality Assessments

A. Product Overview

This submission (NDA 209401) is a 505(b)(2) application, referencing NDA 021041 for DepoCyt (cytarabine) and NDA 050704 DaunoXome (daunorubicin). The applicant is relying on the published literature and the FDA's prior findings of clinical pharmacology (i.e., metabolism and excretion pathways and drug-drug interactions with cardiotoxic agents and hepatotoxic agents) and nonclinical pharmacology/toxicology (i.e., mechanisms of action, genotoxicity, carcinogenicity, reproductive, and developmental toxicity) for the listed drugs, DepoCyt Injection, and DaunoXome Injection.
The proposed product is a sterile lyophilized liposome dispersion presented in a single-dose 50 mL Type (b) (4) glass vial with grey (b) (4) rubber stoppers and aluminum flip-off caps. The proposed drug product is to be reconstituted with sterile water for injection and further diluted in the infusion media (0.9% sodium chloride injection, USP or 5% dextrose injection, USP).

This NDA was given Rare Disease, Fast Track, Orphan Designation, and Breakthrough Therapy Designation. The NDA was received as a rolling submission, with the CMC section submitted on March 31, 2017.

In this addendum, the updates to the labeling are evaluated and summarized in the executive summary. Updates to the Review 1 are shown in *italicized brown fonts* below.

Proposed Indication(s) including Intended Patient Population	VYXEOS is a liposomal combination of (b) (4), cytarabine and daunorubicin, indicated for the treatment of adults with therapy-related Acute

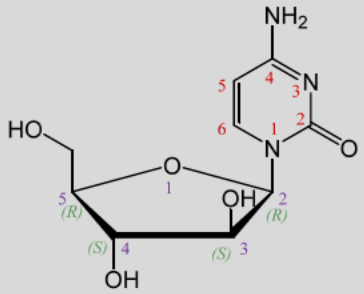
	Myeloid Leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC).
Duration of Treatment	Induction: VYXEOS (cytarabine/daunorubicin) 100 mg/44 mg per m^2 via intravenous infusion over 90 minutes (b) (4) on days 1, 3, and 5 and on days 1 and 3 for subsequent cycles of induction, if needed. Consolidation: VYXEOS (cytarabine/daunorubicin) 65mg/29 mg per m^2 via intravenous infusion over 90 minutes (b) (4) on days 1 and 3
Maximum Daily Dose	***NA***
Alternative Methods of Administration	***NA***

B. Quality Assessment Overview

Drug substance:

Cytarabine:

Cytarabine is a chiral, white or almost white crystalline powder freely soluble in water but slightly soluble in ethanol or methylene chloride. No information on polymorphism is provided in the submission. The applicant provided reference for the DMF (b) (4) ((b) (4) DMF (b) (4) ((b) (4) .), and DMF (b) (4) ((b) (4)). The drug substance from (b) (4) and (b) (4) were used for developmental studies, while the drug substance from (b) (4) will be used for commercial manufacturing.



4-amino-1-((2*R*,3*S*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)pyrimidin-2(1*H*)-one

Chemical Formula: $C_9H_{13}N_3O_5$

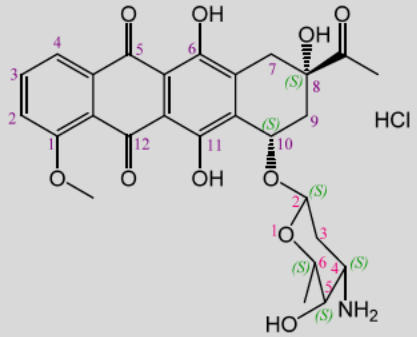
Molecular Weight: 243.22

The applicant has provided spectroscopic evidence for the structure of cytarabine. The applicant has referred to the (b) (4) DMF (b) (4) for the manufacturing and controls, batch analysis and stability data of the drug substance. The DMF (b) (4) is currently adequate to support this NDA.

The applicant provided batch analysis data for cytarabine manufactured by (b) (4) and a comparability report with the API manufactured by (b) (4) The drug substance batches manufactured at the two sites were found to be equivalent.

Daunorubicin:

Daunorubicin HCl is an orange-red, hydroscopic crystalline powder freely soluble in water and methanol, but slightly soluble in ethanol and practically insoluble in acetone. No information is provided regarding polymorphism in this submission. The applicant provided reference for the DMF (b) (4) ((b) (4) and DMF (b) (4) ((b) (4)). The drug substance from (b) (4) was used for developmental studies, while the drug substance from (b) (4) will be used for commercial manufacturing.



(8*S*,10*S*)-8-acetyl-10-(((2*S*,4*S*,5*S*,6*S*)-4-amino-5-hydroxy-6-methyltetrahydro-2*H*-pyran-2-yl)oxy)-6,8,11-trihydroxy-1-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione hydrochloride

Chemical Formula: $C_{27}H_{30}ClNO_{10}$

Molecular Weight: 563.98

The applicant has referred the DMF (b) (4) for more information on general properties, manufacturing properties and controls, batch analysis and stability data. The applicant also referred to the DMF for spectroscopic characterization of the drug substance and a list of impurities. The DMF (b) (4) is currently adequate to support this NDA.

The applicant provided batch analysis data for cytarabine manufactured by (b) (4) and a comparability report with the API manufactured by (b) (4) The drug substance batches manufactured at the two sites were found to be equivalent.

Drug Product:

CPX-351 Liposome for Injection is a sterile lyophilized liposome formulation intended for parenteral administration. The drug product is packaged in a 50 mL USP/Ph.Eur Type (b) (4) colorless glass vial, sealed with a 20 mm (b) (4) grey (b) (4) stopper with (b) (4) and sealed with a 20 mm gray aluminum flip off seal. Each single-dose 50 mL vial contains 100 mg cytarabine and 44 mg daunorubicin in a 5:1 molar ratio.

Apart from the two drug substances, the drug product is composed of the lipid components (distearoylphosphatidylcholine (DSPC), distearoylphosphatidylglycerol (DSPG), and cholesterol), copper gluconate (1 (b) (4)), sucrose ((b) (4)), triethanolamine ((b) (4)), and (b) (4)). No novel excipients are used in the formulation.

All excipients used for the manufacture of the proposed drug product are compendial except DSPC, DSPG, and (b) (4). The specifications for compendial excipients are equivalent to, or tighter than the requirements of the USP/NF. Additional testing and relevant analytical method validation is provided by the applicant.

Cholesterol HP is derived from the [redacted], and a BSE/TSE free statement is provided from the supplier. The applicant provides letters to cross reference active DMFs for cholesterol, DSPC, and DSPG which were reviewed and found adequate to support this NDA. The applicant has provided an adequate description of the drug product composition, formulation development, excipient compatibility, specifications, analytical methods, and container closure information.

The drug product manufacturing process involves [redacted]

The proposed drug product specifications include testing for appearance, reconstitution time, [redacted] pH of the reconstituted suspension, particle size, osmolality, particulate matter, identification for each of the drug substances, assay, % encapsulation, and impurities for each API, assay and impurities for each of the liposome components (DSPC, DSPG, and cholesterol), copper assay, [redacted] impurities, [redacted] endotoxin, sterility, and *in vitro* release for each API.

Registration stability data provided in the NDA supports the proposed shelf life of 48 months at 5±3 °C. The compatibility of the formulation with the container closure system is supported by stability data. Compatibility upon reconstitution and dilution in infusion solutions is supported by in-use stability and leachables studies. The applicant provided adequate post-approval commitments.

The applicant is requesting categorical exclusion from EA under 21 CFR 25.31(b). The applicant provided calculations to show that the estimated concentration of the active moieties at the point of entry into the aquatic environment is less than 1 ppb.

Labeling:

The applicant provided updated labeling to reflect the change in order of the drug substance in the proprietary name. Daunorubicin is listed first followed by cytarabine throughout the PI. While this is reverse alphabetical order, the OND recommended this order as the dosing is based on daunorubicin amounts. The applicant also replaced "[redacted]" in the carton container for both the presentations (2 vials and 5 vials) with "interchange" to be consistent with the wording in the boxed warning of the PI. This change was made at the request of the review team. The labeling is now ***acceptable*** *from the CMC perspective.*

Facilities:

Cytarabine, USP drug substance is manufactured and tested (stability) by [redacted]. This site was last inspected in [redacted]. This facility is determined acceptable based on inspectional history. Daunorubicin, USP drug substance is manufactured and tested (stability) by [redacted]

(b) (4)). This site was last inspected in (b) (4). This facility is determined acceptable based on inspectional history. Both the drug substances are tested (release) by (b) (4). This site was last inspected in (b) (4). This facility is determined acceptable based on inspectional history. The drug product is manufactured, packaged, and tested (both release and stability) by (b) (4). Based on the pre-approval inspection evaluation and the firm's response to the 8-item 483 and RAI, the facility was found acceptable. However, a ***post-approval inspection is recommended*** to evaluate the amended PPQ study and report, effectiveness of aseptic operations corrective actions, execution and interpretation of media fills, improvements to equipment oversight and maintenance, and optimization of the lipid impurities method. ***The applicant has also agreed to provide the revalidation data for the lipid impurities method via a general correspondence to the NDA when available (expected November 2017).***
The drug product is tested (for copper) by (b) (4). This site was last inspected in (b) (4). This facility is determined acceptable based on inspectional history. The drug product is labeled and secondary packaged by (b) (4) and (b) (4). This sites were last inspected in (b) (4) and (b) (4) respectively. These facilities were determined acceptable based on inspectional history.

Biopharmaceutics:
Based on recommendations of the Biopharmaceutics Reviewer, the applicant proposed a harmonized 3-point In Vitro Release (IVR) acceptance criteria for both the APIs. The acceptance criterion at the first time point of 1h was proposed as NMT (b) (4)%, second time point of 6h was proposed as (b) (4)%, and the third time point of 72h as NLT (b) (4)%. The proposed method consists of USP apparatus 2 equipped with mini-vessels and PTFE coated mini-paddles rotating at 75 rpm. The 150 mL IVR media consisting of 25 mM ammonium acetate with 1.8% sodium chloride buffer at pH 4, 0.10% polysorbate and 0.001% doxorubicin hydrochloride is maintained at 37°C. To separate encapsulated and free drugs, the samples are microcentrifuged using a diafilter device. The applicant has provided data to show that the IVR method has sufficient discriminating power and is stability indicating.

C. Special Product Quality Labeling Recommendations (NDA only)

None

D. Final Risk Assessment (Refer to Review 1)

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Anamitro Banerjee

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ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment - NDA

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Sterility	• Formulation • Container closure • Process parameters • Scale/equipments • Site	H	(b) (4) Tested in specifications per USP <71>	Acceptable	None
Endotoxin Pyrogen	• Formulation • Container closure • Process parameters • Scale/equipments • Site	M	Tested in specifications per USP <85>	Acceptable	None
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L	daunorubicin and cytarabine tested in specifications	Acceptable	None
Physical stability (solid state)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L	Demonstrated on shelf life; and studies conducted during development	Acceptable	None
Assay (preservative)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	L	No preservative is used in DP; DP is packaged in single-dose vials	Acceptable	None
Assay (anti-	• Formulation	L	No	Acceptable	None

oxidant)	• Raw materials • Process parameters • Scale/equipment • Site		antioxidant is used in DP		
Uniformity of Dose (Fill volume/deliverable volume)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	L	Tested in specifications per USP <905>	Acceptable	None
Osmolality	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	Tested in specifications	Acceptable	None
pH (High)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L	pH tested in specifications with acceptance of (b) (4)	Acceptable	None
pH (Low)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L	pH tested in specifications with acceptance of (b) (4)	Acceptable	None
Particulate Matter	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	M	Tested in specifications	Acceptable	None
Leachables extractables	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L	Extractables and leachables studies conducted for container closure and IV bags	Acceptable	None
Re-dispersability/reconstitution time	• Formulation • Process parameters • Scale/equipment • Site	M	Tested in specifications with reconstitution time of NMT (b) (4) min	Acceptable	None
Moisture content	• Formulation • Container closure • Process parameters • Scale/equipment • Site	L	Tested in specifications	Acceptable	None
Appearance	• Formulation	M	Tested in	Acceptable	None

(caking)	• Container closure • Process parameters • Scale/equipment • Site		specifications for lyophilized cake and reconstituted solution		
Appearance (color/turbidity)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	Tested in specifications for lyophilized cake and reconstituted solution	Acceptable	None
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	(b) (4) daunorubicin and cytarabine tested in their specifications	Acceptable	None
In Vitro Drug Release	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	M	Tested in specifications	Acceptable	IVR profile comparability should be demonstrated to support SUPAC-MR changes.
Liposome Particle Size Distribution	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	M	Tested in specifications	Acceptable	Conformance to the approved PSD acceptance criteria should be demonstrated to support SUPAC-MR changes.

Anamitro Banerjee -S

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Christina Capacci-Daniel

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Derek Smith

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Recommendation: APPROVAL

NDA 209401
Review #1

Drug Name/Dosage Form	VYXEOS (Cytarabine and Daunorubicin) Liposome Injection/Lyophilized liposome dispersion
Strength	44 mg daunorubicin and 100 mg cytarabine
Route of Administration	Injection
Rx/OTC Dispensed	Rx
Applicant	Celator Pharmaceuticals, Inc. (a Jazz Pharmaceuticals company)
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
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Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY

		REVIEWER
Drug Substance	Monica Cooper Charles Jewell	Ben Stevens
Drug Product	Paresma Patel	Anamitro Banerjee
Process	Kumar Janoria	Edwin Jhao
Microbiology	David Bateman	Jessica Chiaruttini
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Regulatory Business Process Manager	Teshara Bouie	NA
Application Technical Lead	Anamitro Banerjee	NA
Laboratory (OTR)	Michael Hadwiger	
ORA Lead	Dennis Cantellops	
Environmental	NA	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Adequate	06-Jun-2017	Adequate
	Type II			Adequate	18-Jul-2017	Adequate
	Type II			Adequate	09-June-2017	Adequate
	Type IV			Adequate	09-June-2017	Adequate
	Type IV			Adequate	07-July-2017	Adequate
	Type III					Sufficient information provided
	Type III					Sufficient information provided
	Type V			Adequate	August 25, 2015	

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	72939	CPX-351
NDA	021041	DEPOCYT
NDA	050704	DAUNOXOME

2. CONSULTS

None

Executive Summary

I. Recommendations and Conclusion on Approvability

The NDA209401 is recommended for APPROVAL from the CMC point of view. The quality information provided in this NDA is acceptable
The final labeling evaluation is pending as the OND requested the applicant to update the order of API in the labeling. The updated carton labeling reflecting the order of API will be evaluated when available.

Action letter language (to be communicated to the applicant):
An expiration dating period of 48 months is granted for this product when stored at 2 ℃ to 8 ℃ (36 ℉ to 46 ℉) protected from light.

II. Summary of Quality Assessments

A. Product Overview

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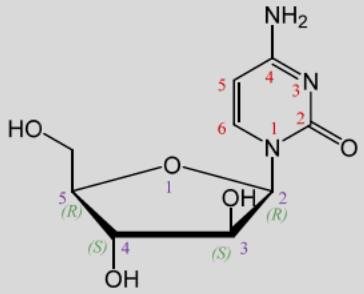
Duration of Treatment	Induction: VYXEOS (cytarabine/daunorubicin) 100 mg/44 mg per m^2 via intravenous infusion over 90 minutes (b) (4) on days 1, 3, and 5 and on days 1 and 3 for subsequent cycles of induction, if needed. Consolidation: VYXEOS (cytarabine/daunorubicin) 65mg/29 mg per m^2 via intravenous infusion over 90 minutes (b) (4) on days 1 and 3
Maximum Daily Dose	***NA***
Alternative Methods of Administration	***NA***

B. Quality Assessment Overview

Drug substance:

Cytarabine:

Cytarabine is a chiral, white or almost white crystalline powder freely soluble in water but slightly soluble in ethanol or methylene chloride. No information on polymorphism is provided in the submission. The applicant provided reference for the DMF (b) (4) ((b) (4) DMF (b) (4) ((b) (4) S.p.A.), and DMF (b) (4) ((b) (4) The drug substance from (b) (4) and (b) (4) were used for developmental studies, while the drug substance from (b) (4) will be used for commercial manufacturing.



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Daunorubicin:

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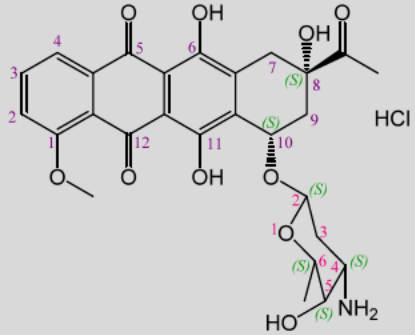

(8*S*,10*S*)-8-acetyl-10-(((2*S*,4*S*,5*S*,6*S*)-4-amino-5-hydroxy-6-methyltetrahydro-2*H*-pyran-2-yl)oxy)-6,8,11-trihydroxy-1-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione hydrochloride

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Apart from the two drug substances, the drug product is composed of the lipid components (distearoylphosphatidylcholine (DSPC), distearoylphosphatidylglycerol (DSPG), and cholesterol), copper gluconate ((b) (4) sucrose (b) (4), triethanolamine (b) (4)), and (b) (4) . No novel excipients are used in the formulation. All excipients used for the manufacture of the proposed drug product are compendial except DSPC, DSPG, and (b) (4). The specifications for compendial excipients are equivalent to, or tighter than the requirements of the USP/NF. Additional testing and relevant analytical method validation is provided by the applicant. Cholesterol HP is derived from the (b) (4) and a BSE/TSE free statement is provided from the supplier. The applicant provides letters to cross reference active DMFs for cholesterol, DSPC, and DSPG which were reviewed and found adequate to

support this NDA. The applicant has provided an adequate description of the drug product composition, formulation development, excipient compatibility, specifications, analytical methods, and container closure information.

The drug product manufacturing process involves (b) (4)

The proposed drug product specifications include testing for appearance, reconstitution time, (b) (4) pH of the reconstituted suspension, particle size, osmolality, particulate matter, identification for each of the drug substances, assay, % encapsulation, and impurities for each API, assay and impurities for each of the liposome components (DSPC, DSPG, and cholesterol), copper assay, (b) (4) impurities, (b) (4) endotoxin, sterility, and *in vitro* release for each API.

Registration stability data provided in the NDA supports the proposed shelf life of 48 months at 5±3 °C. The compatibility of the formulation with the container closure system is supported by stability data. Compatibility upon reconstitution and dilution in infusion solutions is supported by in-use stability and leachables studies. The applicant provided adequate post-approval commitments.

The applicant is requesting categorical exclusion from EA under 21 CFR 25.31(b). The applicant provided calculations to show that the estimated concentration of the active moieties at the point of entry into the aquatic environment is less than 1 ppb.

Facilities:

Cytarabine, USP drug substance is manufactured and tested (stability) by (b) (4). This site was last inspected in (b) (4). This facility is determined acceptable based on inspectional history. Daunorubicin, USP drug substance is manufactured and tested (stability) by (b) (4) (FEI (b) (4)). This site was last inspected in (b) (4). This facility is determined acceptable based on inspectional history. Both the drug substances are tested (release) by (b) (4). This site was last inspected in August 2016. This facility is determined acceptable based on inspectional history. The drug product is manufactured, packaged, and tested (both release and stability) by (b) (4)). Based on the pre-approval inspection evaluation and the firm's response to the 8-item 483 and RAI, the facility was found acceptable. However, a ***post-approval inspection is recommended*** to evaluate the amended PPQ study and report, effectiveness of aseptic operations corrective actions, execution and interpretation of media fills, improvements to equipment oversight and maintenance, and optimization of the lipid impurities method. ***The applicant has also agreed to provide the revalidation data for the lipid impurities method via a general correspondence to the NDA when available (expected November 2017).***

The drug product is tested (for copper) by (b) (4) This site was last inspected in (b) (4). This facility is determined acceptable based on inspectional history. The drug product is labeled and secondary packaged by (b) (4) and (b) (4) . This sites were last inspected in (b) (4) and (b) (4) respectively. These facilities were determined acceptable based on inspectional history.

Biopharmaceutics:
Based on recommendations of the Biopharmaceutics Reviewer, the applicant proposed a harmonized 3-point In Vitro Release (IVR) acceptance criteria for both the APIs. The acceptance criterion at the first time point of 1h was proposed as NMT (b) (4)%, second time point of 6h was proposed as (b) (4)%, and the third time point of 72h as NLT (b) (4)%. The proposed method consist P apparatus 2 equipped with mini-vessels and PTFE coated mini-paddles rotating at 75 rpm. The 150 mL IVR media consisting of 25 mM ammonium acetate with 1.8% sodium chloride buffer at pH 4, 0.10% polysorbate and 0.001% doxorubicin hydrochloride is maintained at 37°C. To separate encapsulated and free drugs, the samples are microcentrifuged using a diafilter device. The applicant has provided data to show that the IVR method has sufficient discriminating power and is stability indicating.

C. Special Product Quality Labeling Recommendations (NDA only)

None

D. Final Risk Assessment (see Attachment)

E. List of Deficiencies for Complete Response

None

Application Technical Lead Name and Date: Anamitro Banerjee, Ph.D. July 28, 2017

Anamitro Banerjee

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LABELING

Note: The applicant was asked to change the order of drug substances to read Vyxeos (daunorubicin and cytarabine) liposome for injection. [redacted] The CMC team defers to the clinical division (DHP) and DMEPA regarding the order of drug substances. The final PI labeling and final carton/container labeling will be evaluated if changes are made, and a memo will be filed at a later date.

The following information requests were sent to the applicant on 13-June-2017 and responses received on 22-June-2017 (SD30):

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

Response: The applicant removed the term [redacted] from the carton/container labels and the PI labeling.
Evaluation: The applicant made the requested changes and the PI and carton/container labeling present the strength of the drug product as the "mg" quantities of the two active ingredients. The most recent labels and labeling are reviewed in detail below. ***Adequate.***

- 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 "[redacted]" 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.

Response: The applicant revised [redacted] to single-dose on the carton/container labels and the PI labeling.
Evaluation: ***Adequate.***

I. Package Insert, Submitted 21-July-2017

1. *Highlights of Prescribing Information*

DOSAGE FORMS AND STRENGTHS

[redacted] For Injection: [redacted] 44 mg daunorubicin and 100 mg cytarabine encapsulated in liposomes ~~and~~ as a lyophilized cake in a single-dose vial for reconstitution. (3)

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	X
Dosage form, route of administration	X
Controlled drug substance symbol (if applicable)	N/A
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	X

Reviewer's Assessment: *Adequate.*
The applicant made the proposed changes in the Highlights section with the exception of the order of the drug substances. The CMC team defers to clinical and DMEPA regarding the order of drug substances.

2. ***Dosage and Administration (Section 2.3)***

2.3 Preparation and Handling

VYXEOS is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1] VYXEOS is supplied as a single-dose vial and does not contain any preservatives. Do not save any unused portions for later administration.

Preparation Instructions:

- Calculate the VYXEOS dose based on daunorubicin and [redacted] (b) (4) individual patient's BSA.
- Calculate the number of vials of VYXEOS based on the daunorubicin dose
- Remove the appropriate number of vials of VYXEOS from the refrigerator.
- Reconstitute each vial with 19 mL of Sterile Water for Injection using a sterile syringe.
- Do not heat, vortex, or shake vigorously.
- After reconstitution, [redacted] (b) (4) let rest for 15 minutes.
- The reconstituted product should be an opaque, purple, homogeneous dispersion, essentially free from visible particulates. After reconstitution (but before final dilution) ~~E~~each mL [redacted] (b) (4) will contain 2.2 mg of daunorubicin and 5 mg of cytarabine [redacted] (b) (4).
- [redacted] (b) (4) prior to withdrawing the reconstituted product for further dilution. If the reconstituted product is not diluted into an infusion bag immediately, [redacted] (b) (4) store in refrigerator at 2ºC to 8ºC for up to 4 hours.
- Calculate the volume of reconstituted VYXEOS required using the following formula:

  [volume required (mL) = dose of [redacted] (b) (4) daunorubicin (mg/m^2) X patient's BSA (m^2) / [redacted] (b) (4) 2.2 (mg/mL)]
- Aseptically withdraw the calculated volume of the reconstituted product from the vial(s) with a sterile syringe and transfer it to an infusion bag containing 500 mL of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. There may be residual product remaining in the vial. Discard unused portion.
- Gently invert the bag to mix the solution. The dilution of the reconstituted product results in a deep purple, translucent, homogeneous dispersion, free from visible particulates.
- If the diluted infusion solution is not used immediately, [redacted] (b) (4) store in refrigerator at 2ºC to 8ºC for up to 4 hours.

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Only solutions without visible particles should be used.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	X

Reviewer's Assessment: *Adequate.*
The applicant revised the preparation and handling section [redacted] (b) (4).
The CMC team defers to clinical and DMEPA regarding whether dosing should be based on cytarabine or daunorubicin.

The applicant also updates the reconstitution instructions to be consistent with the methods provided in the NDA. The revised reconstitution procedure is more detailed and acceptable. The applicant edits to the Preparation and Handling Section are highlighted in red below, and are acceptable from the CMC perspective.

2.3 Preparation and Handling Instructions
VYXEOS is a cytotoxic drug. Follow applicable special handling and disposal procedures.1
VYXEOS is supplied as a single-dose vial and does not contain any preservatives. Do not save any unused portions for later administration.

Preparation Instructions:
•Calculate the VYXEOS dose based on [redacted] (b) (4) and individual patient's BSA.
•Calculate the number of vials of VYXEOS based on the [redacted] (b) (4) dose.
•Remove the appropriate number of vials of VYXEOS from the refrigerator and equilibrate to the room temperature for 30 minutes.
•Then, reconstitute each vial with 19 mL of Sterile Water for Injection using a sterile syringe and immediately thereafter start a 5-minute timer.
•Carefully swirl the contents of the vial for 5 minutes while gently inverting the vial every 30 seconds.
•Do not heat, vortex, or shake vigorously.
•After reconstitution, let rest for 15 minutes.
•The reconstituted product should be an opaque, purple, homogeneous dispersion, essentially free from visible particulates. After reconstitution (but before final dilution), each mL will contain 5 mg of cytarabine and 2.2 mg of daunorubicin.
•Gently invert each vial 5 times prior to withdrawing the reconstituted product for further dilution. If the reconstituted product is not diluted into an infusion bag immediately, store in refrigerator at 2ºC to 8ºC for up to 4 hours.
•Calculate the volume of reconstituted VYXEOS required using the following formula:
[volume required (mL) = dose of [redacted] (b) (4) (mg/m^2) X patient's BSA (m^2) ÷ (b) (4) (mg/mL)]
•Aseptically withdraw the calculated volume of the reconstituted product from the vial(s) with a sterile syringe and transfer it to an infusion bag containing 500 mL of 0.9% Sodium Chloride

Injection, USP or 5% Dextrose Injection, USP. There may be residual product remaining in the vial. Discard unused portion.
•Gently invert the bag to mix the solution. The dilution of the reconstituted product results in a deep purple, translucent, homogeneous dispersion, free from visible particulates.
•If the diluted infusion solution is not used immediately, store in refrigerator at 2ºC to 8ºC for up to 4 hours.
•Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Only solutions without visible particles should be used.

3. *Dosage Forms and Strengths (Section 3)*

VYXEOS (b) (4) is (b) (4) a sterile, preservative-free, purple, lyophilized, (b) (4) cake for reconstitution supplied in a single-dose clear glass vial as follows:

- For injection: 44 mg daunorubicin and 100 mg cytarabine encapsulated in liposomes (b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	X
Strengths: in metric system	X
Active moiety expression of strength with equivalence statement (if applicable)	X
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	X

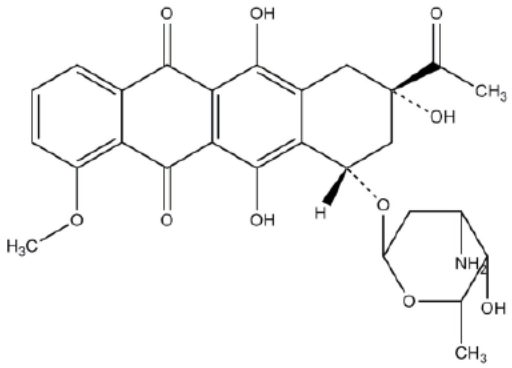
Reviewer's Assessment: *Adequate.*
The applicant made the proposed changes, shown in red above, in the Dosage Forms and Strengths section (b) (4). The CMC team defers to clinical and DMEPA regarding the order of drug substances.

4. *Description (Section 11)*

VYXEOS (daunorubicin and cytarabine (b) (4)) liposome for injection is a combination of daunorubicin and cytarabine (b) (4) in a 1:5 (b) (4) molar ratio encapsulated in (b) (4) liposomes for intravenous administration. (b) (4) The liposome membrane is composed of

distearoylphosphatidylcholine (DSPC), distearoylphosphatidylglycerol (DSPG), and cholesterol in a 7:2:1 molar ratio.

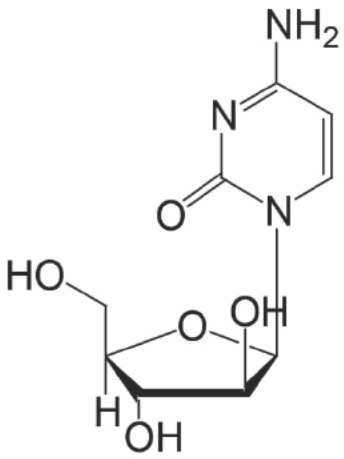
Daunorubicin is an anthracycline topoisomerase inhibitor. The chemical name for daunorubicin hydrochloride is (1S,3S)-3-acetyl-1,2,3,4,6,11-hexahydro-3,5,12-trihydroxy-10-methoxy-6,11-dioxo-1-naphthacenyl-3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranoside (b) (4); its molecular weight is 527.52 (b) (4) Daunorubicin has the following structural formula:



(b) (4)

(b) (4)

Cytarabine is a nucleoside metabolic inhibitor. The chemical name of cytarabine is 2(1H)-pyrimidione, 4-amino-1-β-D-arabinofuranosyl- (b) (4); its molecular weight is 243.22. Cytarabine has the following structural formula:



(b) (4)

(b) (4)

(b) (4)

VYXEOS liposome for injection is supplied as a sterile, preservative-free, purple, lyophilized cake, in a single-dose vial. Each vial contains 44 mg of daunorubicin and 100 mg cytarabine (b) (4) , and the following inactive ingredients: 454 mg distearoylphosphatidylcholine ~~454 mg~~, 132 mg distearoylphosphatidylglycerol ~~132 mg~~, 32 mg cholesterol HP ~~32 mg~~, 100 mg copper gluconate ~~100 mg~~, 4 mg triethanolamine ~~4 mg~~, and 2054 mg sucrose ~~2054 mg~~.

(b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	X
Dosage form and route of administration	X
Active moiety expression of strength with equivalence statement (if applicable)	X
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	X
Statement of being sterile (if applicable)	X
Pharmacological/ therapeutic class	X
Chemical name, structural formula, molecular weight	X
If radioactive, statement of important nuclear characteristics.	N/A
Other important chemical or physical properties (such as pKa or pH)	X

Reviewer's Assessment: ***Adequate.***
The applicant made the proposed changes, shown in red above, in the Description section with the exception of the order of the drug substances. The CMC team defers to clinical and DMEPA regarding the order of drug substances.

A correction to the chemical name of cytarabine is shown below, and will be communicated to the applicant. The proposed change is consistent with other approved cytarabine products.
Chemical name of cytarabine:
4-amino-1-β-D-arabinofuranosyl-2(1H)-pyrimidinone, (b) (4)

5. *How Supplied/Storage and Handling (Section 16)*

How Supplied

VYXEOS™ (daunorubicin and cytarabine [redacted]) liposome for injection is supplied as a sterile, preservative-free, purple, lyophilized cake, [redacted] in a single-dose vial. Each VYXEOS vial (NDC 68727-745-01) contains 44 mg daunorubicin and 100 mg cytarabine [redacted]

NDC 68727-745-02: Carton containing 2 vials of VYXEOS

NDC 68727-745-05: Carton containing 5 vials of VYXEOS

Storage

Store unreconstituted VYXEOS vials in a refrigerator at 2°C to 8°C (36°F to 46°F) in an upright position. The vial should be stored in its original carton to protect from light.

Handling and Disposal

VYXEOS is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	X
Available units (e.g., bottles of 100 tablets)	X
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	X
Special handling (e.g., protect from light)	X
Storage conditions	X
Manufacturer/distributor name (21 CFR 201.1(h)(5))	X (provided after section 17)

Reviewer's Assessment: ***Adequate.***
[redacted]. The CMC team defers to clinical and DMEPA regarding the order of drug substances.

II. Labels:

The most recent container label and carton labeling were submitted on 19-July-2017 (SD42), and are copied and evaluated below.

The following information requests and comments were sent to the applicant during review of the NDA. The Agency comments, applicant response, and evaluation are shown below.
Container Label and Carton Labeling Comments sent on 07-July-2017, Response Received on 13-July-2017 (SD37):

- 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.

Response: The applicant proposes [redacted] (b) (4) .

Evaluation: The CMC team defers the decision regarding order of drug substances to the clinical division DHP and DMEPA. The order of drug substances for the container label and carton labeling should be consistent with the package insert. If changes are made, the final PI and carton/container labeling will be evaluated for consistency. ***CMC defers the order of drug substances in the labeling to the DHP clinical team.***

- Remove [redacted] (b) (4)" and the [redacted] (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.

Response: The applicant removed [redacted] (b) (4) from the container label and carton labeling.

Evaluation: ***Adequate.***

- Move the route of administration statement "FOR INTRAVENOUS [redacted] (b) (4) ONLY" right underneath the strength presentation.

Response: The applicant moved the statement "FOR INTRAVENOUS [redacted] (b) (4)" to be below the strength presentation.

Evaluation: The applicant was also asked to revise the statement to read "For Intravenous Infusion Only." Refer to the IR below. ***Adequate.***

Carton Labeling Comments sent on 07-July-2017, Response Received on 13-July-2017 (SD37):

- 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."

Response: The applicant revised the ingredient listing to be consistent with the PI. The applicant proposes [redacted] (b) (4)

Evaluation: The applicant has revised the listing of inactive ingredients on the carton labeling [redacted] (b) (4) The CMC team defers to the clinical division DHP regarding the order of drug substances. The inactive ingredients listing is acceptable. ***Adequate.***

- Display the net quantity and sterility statement (i.e. Contains 2 Sterile Single-dose vials) on the PDP instead of the side panel.

Response: The applicant moved the net quantity and sterility statement to the PDP.

Evaluation: ***Adequate.***

- Include the statement, "Rx only" on the PDP as required by Section 503(b)(4)(A) of the Federal Food, Drug and Cosmetic Act.

Response: The applicant includes "Rx only" on the PDP and the side panel.
Evaluation: ***Adequate.***

The applicant asked for clarification regarding the placement of liposome relative to the drug substances. The applicant question and Agency response were sent to the applicant on 17-July-2017, and are shown below.

- ***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,* (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."
Applicant Response dated 17-July-2017 (SD42): The applicant made the requested change to have liposome outside of the parentheses. The current container label and carton labeling have been adequately updated.
Evaluation: ***Adequate.***

Container Label and Carton Labeling Comments sent on 17-July-2017, Response Received on 19-July-2017 (SD42):

- We recommend the Applicant revise the container label and carton labeling from "For Intravenous (b) (4) Only" to "For Intravenous **Infusion** Only".

Response: The applicant made the requested change for the container label and the carton labeling.
Evaluation: ***Adequate.***

(b) (4)

Item	Information provided in the container label
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Adequate
Dosage strength	Adequate
Net contents	Adequate
"Rx only" displayed prominently on the main panel	Adequate
NDC number (21 CFR 207.35(b)(3)(i))	Adequate
Lot number and expiration date (21 CFR 201.17)	Adequate
Storage conditions	Adequate
Bar code (21CFR 201.25)	Adequate
Name of manufacturer/distributor	Adequate

2. ***Carton Labeling***

(b) (4)

[redacted]

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Item	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	Adequate
Net contents (21 CFR 201.51(a))	Adequate
Lot number per 21 CFR 201.18	Adequate
Expiration date per 21 CFR 201.17	Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	Adequate
Sterility Information (if applicable)	Adequate
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Adequate
Storage Conditions	Adequate
NDC number (per 21 CFR 201.2)(requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	Adequate
Name of manufacturer/distributor	Adequate
"See package insert for dosage information" (21 CFR 201.55)	Adequate
"Keep out of reach of children" (optional for Rx, required for OTC)	Not Required
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))	Adequate

Reviewer's Assessment of Labels: *Adequate.*
During the review cycle the applicant was asked to make the following edits to the container labels and carton labeling:
-order of drug substances should be modified to be consistent with the PI
- (b) (4) statement was removed as it is not needed for this product
-the term " (b) (4) " was revised to "intravenous infusion only" and moved to the PDP
-"Rx only" statement was included on the PDP in addition to the side panel
-list of inactive ingredients was modified to be consistent with the PI
-net contents statement was moved to the PDP

-presentation of the name was modified to have liposome displayed outside of the parentheses.

Refer to the DMEPA review of this application for details regarding DMEPA comments to the applicant. The CMC team defers to the DHP clinical team and DMEPA regarding the order of drug substances.

The most recent container label and carton labeling was submitted on 19-July-2017 (SD42) and meets all regulatory requirements. If additional changes are made to the PI or carton/container labeling they will be evaluated to assure consistency.

Overall Assessment and Recommendation: Adequate.

Primary Labeling Reviewer Name and Date:

Paresma Patel, Ph.D.
July 26, 2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Anamitro Banerjee, Ph.D.
July 26, 2017

Paresma Patel

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Anamitro Banerjee

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Kumar Janoria

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Maotang Zhou

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CHAPTER VII

BIOPHARMACEUTICS

Product Background:

NDA: 209401-ORIG-1
Submission Type: 505(b)(2) NDA (Priority); referencing DepoCyt® and DaunoXome®
Drug Product Name/Strength: VYXEOS™ [CPX-351 (Cytarabine and Daunorubicin) Liposome for Injection]. Each single use vial contains 100 mg cytarabine, and 44 mg daunorubicin (as free base).
Dosage Form/Route of Administration: lyophilized (liposome) cake for reconstitution with 19 mL Sterile Water For Injection and further dilution with 500 mL 0.9% Sodium Chloride Solution for Injection or 5% Dextrose Solution for Injection; for intravenous infusion over 90 minutes
Proposed Dosage (for Acute Myeloid Leukemia): Induction course 1: 100 mg/m^2 cytarabine and 44 mg/m^2 daunorubicin on Days 1, 3, 5, followed by induction on Days 1 and 3, then by consolidation (b) (4) on Days 1, 3).
Applicant Name: Celator (a Jazz Pharmaceuticals Company)

Review Recommendation:
From the Biopharmaceutics perspective, NDA 209401 for VYXEOS™ (Cytarabine and Daunorubicin) Liposome for Injection is recommended for APPROVAL.

Review Summary:
The proposed *in vitro* drug release (IVR) method and the revised IVR acceptance criteria as shown in the table below are approved for the routine QC of VYXEOS™ (daunorubicin and cytarabine) Liposome for Injection at batch release and during stability testing.

USP Apparatus	Speed	Medium	Volume	Acceptance criteria
2 (with mini-vessels and mini-paddles)	75 rpm	25mM ammonium acetate with 1.8% sodium chloride buffer (pH 4.0 ± 0.02), with 0.10% polysorbate 80 and 0.001% doxorubicin hydrochloride] (37 ± 0.5°C)	150 mL	For both Cytarabine and Daunorubicin: 1.0 hours : NMT (b) (4)% 6 hours: (b) (4)% 72 hours: NLT (b) (4)%

Sample Volume: 1 mL of the reconstituted drug product containing 5 mg/mL cytarabine and 2.2 mg/mL daunoubicin base
Separation of free from encapsulated drug is performed using a diafilter device with microcentrifugation.
For IVR profiling, determine free drug concentrations at predetermined time points (e.g., at 0.5, 1, 2, 4, 6, 24, 48, 72, and 96 hours), as well as total (free plus encapsulated) drug concentrations at the first and last sampling time points only.

Bridging data between CPX-351 formulations are not needed *per se* because the proposed commercial drug product has the same formulation/process steps/manufacturer as the drug product that was used in the pivotal Phase 3 clinical trial.

However, the proposed commercial API suppliers are different from those used for the manufacture of the pivotal Phase 3 clinical trial. Based on the comparative *in vitro* cytarabine and daunorubicin release profiles of Process Validation Batch # 7C002 (produced using the (b) (4) and from the APIs sourced from (b) (4) and (b) (4) respectively), the proposed commercial API source change is not anticipated to impact the *in vivo* performance of the to-be-marketed drug product.

List Submissions reviewed:
SDN-3, 3/31/2017 (Modules 2, 3, and 5 of Rolling Submission)
SDN-9, 5/10/2017 (PPQ Batch #4)
SDN-12, 5/19/2017 (Response to Quality Information Request 1)
SDN-17, 5/30/2017 (Response to Quality Information Request 3)
SDN-26, 6/15/2017 (Response to Quality Information Request 5)

Highlight Key Outstanding Issues from Last Cycle:
Not Applicable

Concise Description of Outstanding Issues:
None

Dissolution Method and Acceptance Criteria

Reviewer's Assessment:

In Vitro Drug Release (IVR) Method – *ADEQUATE*

The proposed QC dissolution method consists of USP Apparatus 2 (equipped with small-volume vessels and PTFE coated mini-paddles) rotating at 75 rpm; 150 mL of IVR media [25mM ammonium acetate with 1.8% sodium chloride buffer, pH 4.0 ± (b) (4) with 0.10% polysorbate 80 and 0.001% doxorubicin hydrochloride], maintained at 37 ± 0.5 °C. One mL of the reconstituted drug product sample is added to each dissolution vessel. To separate the encapsulated from the free drugs, samples are microcentrifuged (in a (b) (4)) at (b) (4)
Free or unencapsulated drug concentrations are measured from the samples at protocol pre-specified time points (e.g., at 0.5, 1, 2, 4, 6, 24, 48, 72, and 96 hours); total (free plus encapsulated) drug concentrations are measured at the first and last sampling time points only. [Note that previously, IVR profiles of clinical/stability/developmental drug product batches were determined using (b) (4) urs

(b) (4)

Note also that the Applicant abandoned (b) (4)
IVR method (and invalidated majority of the resulting IVR data) (b) (4)

Rationale for Chosen Drug Release Method Parameters (including biorelevance):

(b) (4)

(b) (4)

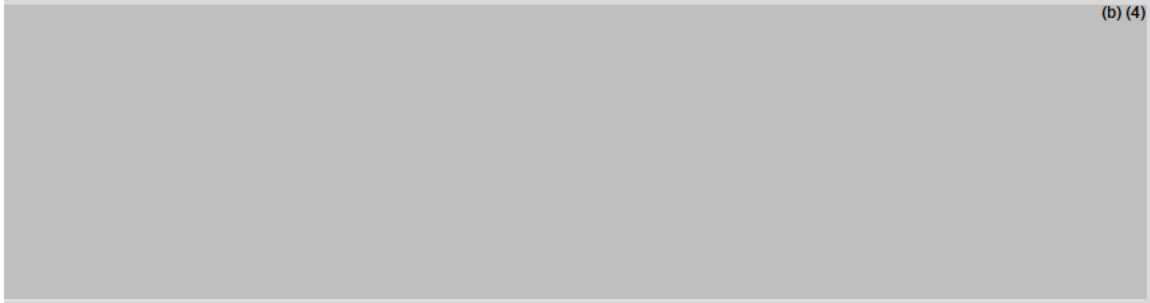
Discriminating Power

Using a 24-hour IVR sampling period, the proposed QC IVR method was shown to be capable of discriminating changes in formulation and manufacturing process.

a) Discriminating for Formulation Variants

Figure 1 compares the IVR profiles of the pivotal Phase 3 clinical trial batches and the two other registration/stability batches to those of [frozen] formulation variants for the following critical material attributes:

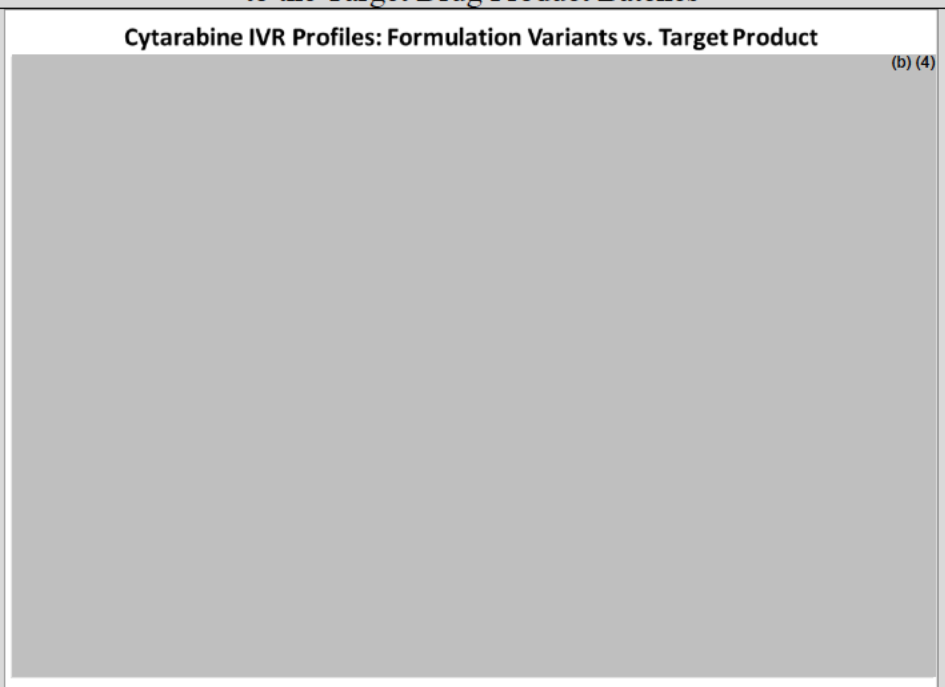
(b) (4)

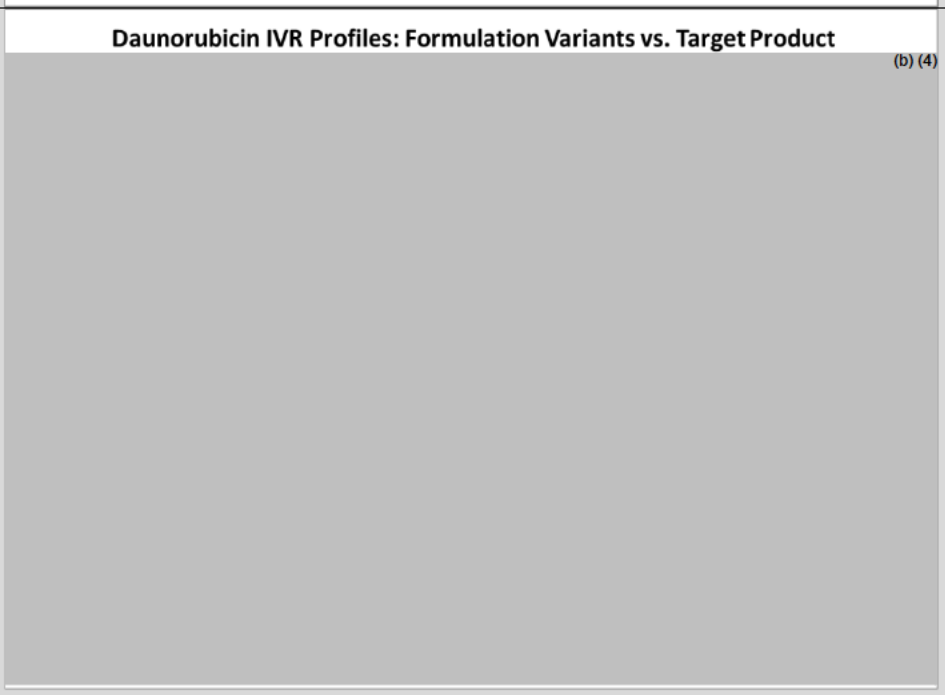


The Reviewer's calculated profile similarity factors (f_2) for all five formulation variants were all < 50, suggesting significant difference in cytarabine and daunorubicin IVR profiles relative to both the Pivotal Phase 3 Clinical Trial Batches #1E003 and #4D007. Note that the IVR profiles of the registration batches were all similar to the reference batches, by f_2 analysis.

Figure 1

Comparison of the Cytarabine and Daunorubicin IVR Profiles of Formulation Variants to the Target Drug Product Batches





Form var = formulation variant

Note: The 4 pivotal Phase 3 clinical trial and primary registration (target product) batches are marked within the yellow shaded area.

b) Disciminating for Manufacturing Variants

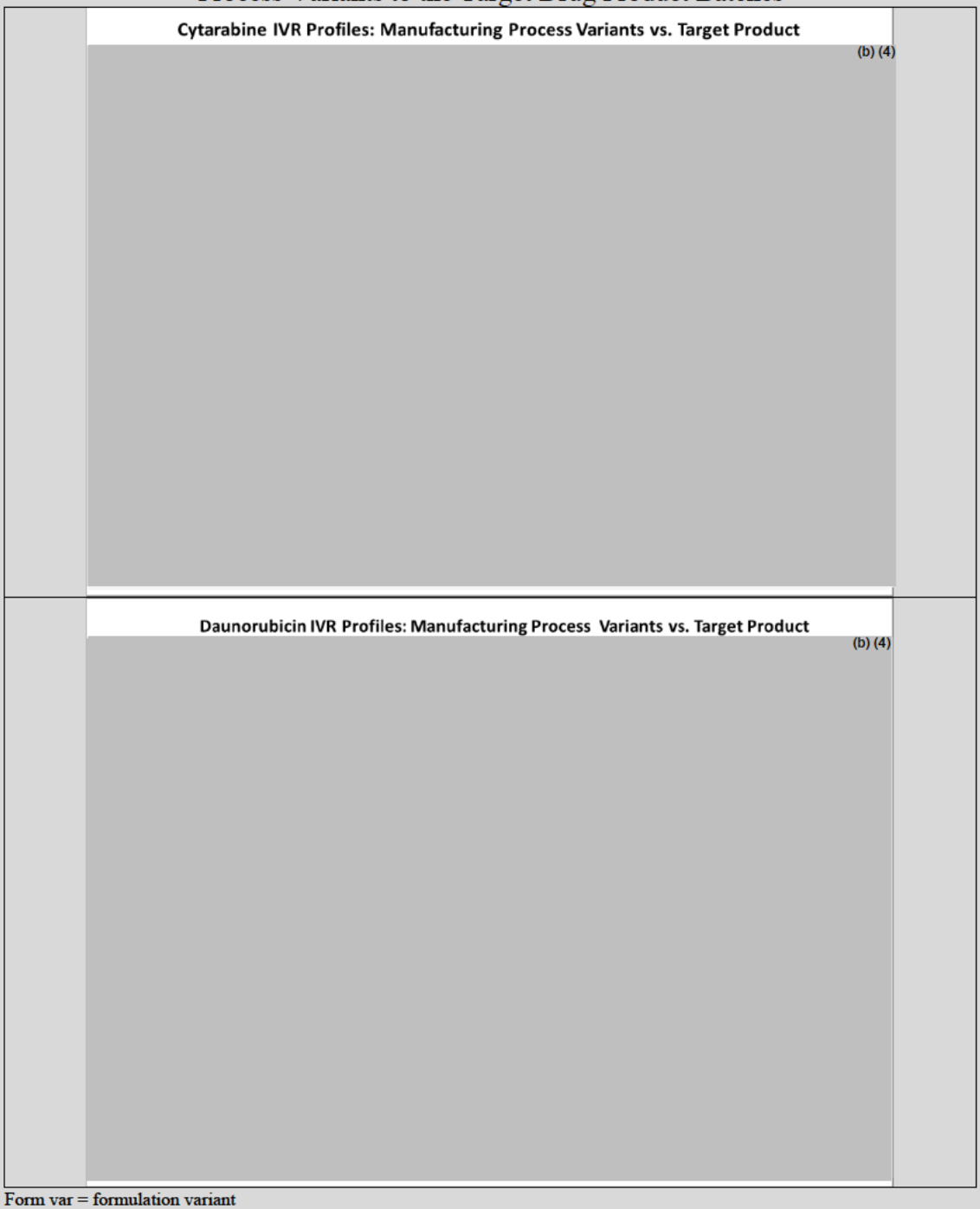
Figure 2 compares the IVR profiles of the pivotal Phase 3 clinical trial and registration/stability batches to those of manufacturing process variants of the lyophilized formulation. The IVR method was able to detect:

(b) (4)

The Reviewer's calculated profile similarity factors (f_2) for all three manufacturing variants were all < 50 with respect to daunorubicin IVR, relative to the Pivotal Phase 3 Clinical Trial Batches #1E003 and #4D007. Additionally, the calculated f_2 value for the variant batch with anomalous particle size distribution was < 50, with respect to cytarabine IVR relative to the reference batches.

Figure 2

Comparison of the Cytarabine and Daunorubicin IVR Profiles of Manufacturing Process Variants to the Target Drug Product Batches



Form var = formulation variant

Note: The 4 pivotal Phase 3 clinical trial and primary registration (target product) batches are marked within the yellow shaded area.

[**Drug Substance** QC Specifications. (b) (4) Refer to the Drug Substance, Process, and Drug Product Reviews for the evaluation of the respective QC Specifications.]

Analytical Method Validation

(b) (4) HPLC (b) (4) (for cytarabine), and (b) (4) (for daunorubicin and doxorubicin) is used to quantify the two APIs (free and encapsulated in the IVR medium). Per the Applicant, the method was satisfactorily validated for both APIs with respect to linearity, recovery, specificity, precision, robustness (in terms of HPLC and IVR conditions), and successfully transferred from the Analytical R&D Lab at Celator to the QC labs at Celator and (b) (4) Supplementary validation for repeatability and intermediate precision was conducted to account for the change in IVR testing duration (from (b) (4) hours to (b) (4) hours). The IVR method was reported to be robust with respect to paddle rotation speed (75 (b) (4) rpm), bath temperature (37 ± 0.5 °C), and media pH (4.0 ± (b) (4), using an acceptance range of ± (b) (4)% absolute difference from the reference condition. Per the Drug Product Reviewer (Dr. Paresma Patel), the analytical validation of the proposed IVR method is Adequate.

In Vitro Drug Release (IVR) Acceptance Criteria – *REVISED CRITERIA ACCEPTABLE*

For batch release and during stability testing of the proposed drug product, the Applicant's originally proposed (b) (4) IVR acceptance ranges (one set for each API, as shown in Table 1) were based on the calculated mean ± 3SD of the cytarabine and daunorubicin release data at each specification time point for seven commercial-scale batches and twelve process development batches. Note that these proposed QC IVR specification time points ((b) (4) proposed tolerance limits) are the same for

cytarabine and daunorubicin. IVR testing will follow USP <711> Levels 1 through 3 (L1, L2, L3) requirements.

Table 1
Proposed *In Vitro* Drug Release Acceptance Criteria for Cytarabine and Daunorubicin in CPX-351 Liposomes at Batch Release and During Stability Testing

(b) (4)

This Reviewer notes that the acceptance ranges for the Applicant's (b) (4) specification time points are rather wide; tightening of these acceptance ranges is feasible when considering the observed IVR data provided for the 9 commercial scale batches that were within the Applicant's finished product QC specifications current at the time of batch release. Based mainly on the IVR profile data provided for the pivotal Phase 3 clinical trial batches (Figures 1 and 2 above), this Reviewer recommends a simplified 3-point IVR acceptance criteria applicable to both APIs, as shown in Tables 2A and 2B.

Note that the Reviewer's recommended simplified three-point IVR acceptance criteria for both APIs 1) were based mainly on the IVR profiles of a pivotal Phase 3 clinical trial batch (4D007) that was used in the analytical method validation of the Applicant's currently proposed (b) (4) hour) IVR method (Figure 3), and 2) considered also the IVR data for this batch's stability samples collected within the proposed expiration dating period of 48 months; see Tables 2A and 2B. [This overall strategy for specification setting is deemed justified because 4D007 exhibited relatively stable IVR profile and PSD profile data over 30 months of long-term storage.] Additionally, the recommended (3-point) IVR acceptance criteria would be sufficient to fail all eight formulation and manufacturing process variants with respect to daunorubicin IVR (and 6 of these 8 formulation/manufacturing variants with respect to cytarabine) as shown in Figures 1 and 2 of this Review. Note that a subset of these so called "variant" drug product batches (e.g., 2J004, 3A005 and 3I006) are commercial scale batches that were reported to have failed QC testing at batch release due to "assignable operational causes" including insufficient number of (b) (4)

Note that this Reviewer chose 6 hours (over (b) (4) hours) as the middle specification time point as this would allow all pivotal Phase 3 clinical trial and registration stability batches (the target/reference drug product batches in Figures 1 and 2) to comply with

this Reviewer's recommended IVR acceptance criteria for both daunorubicin and cytarabine (at batch release and during early stability time points) without having to broaden the acceptance range to > (b)(4)%. Additionally, it was observed that if choosing the (b)(4)-hour time point, an accepta e range that overlaps with that for the final specification time point (NLT (b)(4)%) would have to be selected (at least for daunorubicin). Note also that this Reviewer recommends an upper limit for IVR at the first specification time point (1 hour) since the bone marrow is the putative site of action, and thus premature or higher than necessary levels of passive ('burst") drug release from the liposomes in the blood (the site of administration) upon intravenous injection/infusion of CPX-351 should be minimized to avoid as much as possible off-target effects. [The Applicant reported that (b)(4)% of the total cytarabine and daunorubicin loads were shown to be released (i.e., as free/unencapsulated drug) from the liposomes into the plasma of both humans and animal models of leukemia.] The *in vivo* bioavailability of the two APIs of CPX-351 liposomes in the bone marrow (the target site of action) is achieved through a process involving the (active uptake of intact liposomes by bone marrow, followed by) phagocytic/lysosomal "digestion" of the liposomes. Thus, routine QC monitoring for "complete" *in vitro* drug release from the liposomes, i.e., at the later IVR specification time points may be perceived as not critical from a clinical efficacy perspective, but may still be relevant (1) if the phagocytic/lysosomal cellular response in the bone marrow of the leukemia patient is not fully functional, (2) when considering the pre-clinical PK findings that showed "complete bioavailability" of cytarabine and daunorubicin from CPX-351 liposome injections as a result of non-specific distribution to other organs (as reported by the Applicant), and (3) more importantly from a product quality perspective, to ensure batch-to-batch consistency. Coincidentally, this Reviewer's recommended final specification time point (i.e., (b)(4) hours to check for approximately "complete" drug release) corresponds to the (b)(4)-hour separation period between the 1st and the 2nd doses of CPX-351 of each treatm course during the Induction Phase and the Consolidation Phase. Additionally, the use of the same IVR acceptance criteria for both APIs is consistent with the reported "convergence of *in vivo* PK" when the two APIs are co-administered as CPX-351 liposomes.

When using this Reviewer's recommended acceptance criteria for both APIs at the first and middle specification time points (1 hour and 6 hours), all but one of the Process Validation batches and API Comparability lots at batch release passed retrospectively (i.e., 5I008, 6D001, 6G002 7C002 but not 6K001 particularly with respect to the 6-hour data for both cytarabine and daunorubicin IVR). It is important to note that Batch **6K001** (1) was designated by the Applicant as a "failed" Process Validation Batch [PPQ Batch #3] as it was out-of-specification (OOS) with respect to the liposome particle size distribution acceptance criteria current at the time of its batch release testing, and (2) additionally, was not determined by this Reviewer to be similar to pivotal clinical trial batch #4D007; the calculated f_2 values for the IVR profiles of the two APIs were 44 and 45 (with respect to Phase 3 clinical lot #1E003), or 47 and 48 (with respect to Phase 3 clinical lot # 4D007).

Note that during early routine stability testing, the (b)(4)- and 72- hour sampling time

points were not included. Thus, in order to determine the acceptability of the proposed final specification time point (b) (4) hours, i.e., for NLT (b) (4)%), this Reviewer performed simulation to extrapolate the (b) (4) hour IVR data for PPQ Batch #3; the predicted IVR data shows that this particular batch would be expected to have a higher failing rate than typical batches as it will not comply with this Reviewer's recommended target cytarabine and daunorubicin IVR ('NLT (b) (4)%') at the recommended final ((b) (4)-hour) sampling time point at least during Level 2 testing. In other words, to increa e the possibility of rejecting unacceptable batches worse than "failed" PPQ Batch #3 (6K001) during routine QC testing, this Reviewer is not accepting the Applicant's proposed final specification time point of (b) (4) hours . It is also important to note that the IVR data at batch release of the most recent Process Validation Batch **7C002** (manufactured using the (b) (4) and the APIs from the proposed commercial suppliers) comply with this Reviewer's recommended IVR acceptance criteria (i.e., for both APIs at all three specification time points). Additionally, although the Reviewer's evaluation of the appropriate IVR acceptance criteria did not factor in the latest IVR data provided for the 3 registration stability batches, it is acknowledged here that the 57 – 59 month old (and so theoretically "expired") stability samples appear to be still within the Reviewer's recommended acceptance ranges for the first two IVR specification time points (1 hour and 6 hours). Additionally, based on the available IVR data for the (b) (4) hour sampling time point (and the similarity of IVR profiles relative to the pivotal clinical batches), these "aged" registration batches would be anticipated to comply with the tolerance limit (NLT (b) (4)%) at the Reviewer's recommended final specification time point ((b) (4) hours). This Reviewer requestedIVR profile data (including at the (b) (4) and 72- hou ampling time points) of all drug product batches in storage at the curr /future stability time points; however these stability data will not be available in time to meet the regulatory deadlines for this review. .

Figure 3

In Vitro Cytarabine and Daunorubicin Release Profiles of the Pivotal Clinical Trial Batch 4D007, generated using the proposed QC (b) (4) -hour) IVR method

Table 2A

Summary of Observed Cumulative *In Vitro* CYTARABINE (IVR) Release Profile

Data for Proposed CPX-315 Liposomes [%], using the proposed (b) (4)-hour IVR Method[a,b]

	Pivotal Phase 3 Clinical Batch (4D007[a]) [Mean (Range of Individual Unit Values)]	Pivotal Phase 3 Clinical Batch (4D007)[b] (Range of Means)	Registration Batches[c] (Range of Means)	Applicant's Proposed Acceptance Range	Reviewer's Recommended Acceptance Range
Specification Timepoint (h)					

(b) (4)

Table 2B

Summary of Observed Cumulative *In Vitro* DAUNORUBICIN (IVR) Release Profile Data for Proposed CPX-315 Liposomes [%], using the proposed (b) (4)-hour IVR Method[a,b]

	Pivotal Phase 3 Clinical Batch (4D007[a]) [Mean (Range of Individual Unit Values)]	Pivotal Phase 3 Clinical Batch (4D007)[b] (Range of Means)	Registration Batches[c] (Range of Means)	Applicant's Proposed Acceptance Range	Reviewer's Recommended Acceptance Range
Specification Timepoint (h)					

(b) (4)

In response to this Reviewer's series of follow-up information requests, the Applicant

agreed to this Reviewer's recommendation to use a harmonized 3-point IVR acceptance criteria for both APIs as well as the recommended IVR limits for the first specification time point (NMT (b)(4)% at 1 hour). However, based on IVR data for all 8 acceptable commercial scale ba hes of VYXEOS manufactured to date, the Applicant counterproposed a slightly different acceptance range for the middle specification time point (at 6 hours, (b)(4) % instead of (b)(4) %), and a later final specification time point for a Q = (b)(4)% (at 72 hours instead of (b)(4) hours). Thus, this Reviewer requested the Applicant to onduct further analyses to (1) also take into consideration the IVR data generated for "failed" PPQ Batch #3 (6K001), and (2) use a power (instead of a linear) trendline equation to better fit the observed dissolution data at the latter sampling time points, and as such more accurately predict the (b)(4)-hour and 72-hour dissolution data for all commercial scale batches of VYXEOS. Based on the last two responses submitted via email, the Applicant's counterproposed acceptance range for 6 hours would be sufficient to reject "failed" PPQ Batch #3 (6K001) in terms of daunorubicin (but not cytarabine) IVR. Furthermore, IVR data at batch release of "successful" PPQ Batches 5I008 and 6G002 would conform to the cytarabine and daunorubicin IVR acceptance criteria if the Applicant's counterproposed final specification time point of 72 hours (in lieu of the Reviewer's initially recommended (b)(4)-hour specification time point) to achieve drug release of 'NLT (b)(4)%' was selected. Therefore, for practical reasons, the Applicant's counterproposed IVR acceptance criteria for both APIs are deemed acceptable by this Reviewer.

In Vitro Drug Release of Stability Samples

The proposed shelf-life for the CPX-351 drug product in the commercial container closure configuration (single use 50 mL capacity Type (b)(4) olorless glass vial in carton) is 48 months at storage conditions of 5°C ± 3°C.

Per the Applicant, during recommended (refrigerated, 5 ± 3°C) storage for up to (b)(4) months there was no change in liposome particle size distribution and no significant change in the IVR rate although there was a reported slight increase in daunoribicin related impurities (albeit, not OOS).

At 24 months under long term stability (25°C/60%RH) storage, some IVR test results were reported to be OOS (per the specification current at the time of testing), indicative that the IVR method is stability indicating. The drug product was shown to be sensitive to light and storage at a temperature of (b)(4)°C.

Bridging of Formulations

Reviewer's Assessment: *NOT APPLICABLE*

Bridging data between CPX-351 formulations *per se* are not needed because the to-be-marketed lyophilized form of the liposomes was evaluated for efficacy/safety/PK in the "Pivotal" Phase 3 Clinical Trial 301, and in Phase 2 Study 206. Note that Lyophilized Liposome Batches 1E003 and 4D007 were used in the pivotal Phase 3 clinical trial.

In vivo PK data are available to compare the frozen (Ready-to-Thaw-and-Dilute) formulation (manufactured at pilot scale by (b) (4) and used in Phase 1/2 Studies 101, 204 and 205) and the to-be-marketed lyophilized formulation (manufactured at commercial scale [(b) (4) L] by (b) (4), and used in Phase 2/3 Studies 301 and 206). Based on the results of Population PK analysis, the Clinical Pharmacology Reviewer (Dr. Liang Li) confirmed that the CPX-351 change from frozen to lyophilized formulations did not produce clinically significant differences in cytarabine and daunorubicin PK. Note that the Medical Reviewer (Dr. Aviva Krauss) does not recommend inclusion in the labeling of the clinical efficacy/safety outcomes of Phase 2b Study 205 (that used the Frozen CPX-351 formulation) due to the study's apparent lack of statistical power to determine a treatment effect, and/or inability to meet the pre-specified study endpoint.

The corresponding comparative *in vitro* dissolution profiles of the Frozen vs. the Lyophilized clinical trial formulations (generated using the (b) (4) IVR method) are shown in Figure 4. Altogether, the comparative IVR data in Figure 4, and the IVR data of developmental and commercial-scale drug product batches measured before and after lyophilization demonstrate similar *in vitro* drug release characteristics of the two CPX-351 formulations and the lack of effect of the (b) (4) process on cytarabine and daunorubicin IVR profiles. This conclusion is not anticipated to be significantly different when using comparative IVR data generated using the proposed (b) (4)-hour dissolution method. Note that compared to the frozen formulation, the lyo hilized formulation does not contain (b) (4) This formulation change from the frozen/liquid state to the lyophilized state (b) (4)

Figure 4

Comparative *in vitro* cytarabine and daunorubicin release profiles*, as a function of CPX-351 formulation (Frozen/Liquid vs Lyophilized Liposomes) used in Clinical Trials

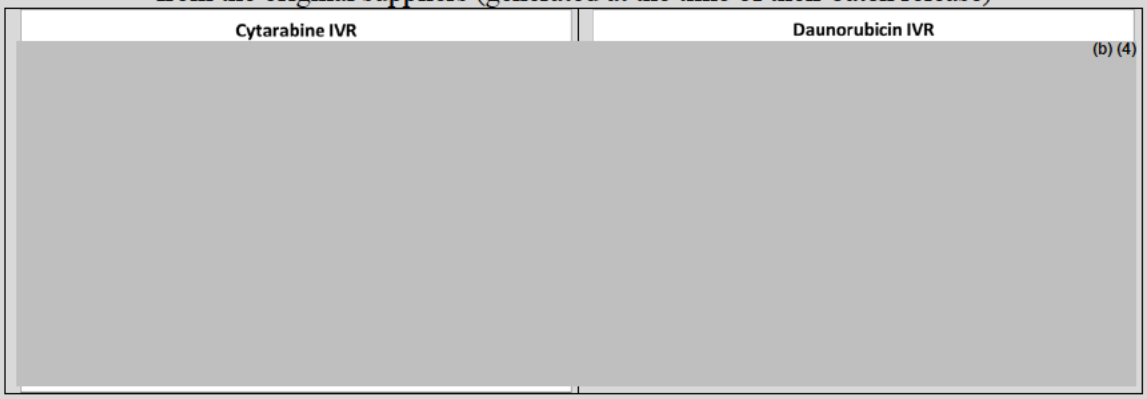
These IVR profiles were generated using the early developmental (b) (4) method consisting of a (b) (4). The Reviewer's calculated profile similarity (f_2) values between the frozen and the lyophilized formulations were >50 for both APIs, suggesting similarity of drug release rates. That the shapes of the drug release profiles were similar suggests the same drug release mechanism for both CPX-351 formulations.

API comparability

To support the pre-marketing change in the suppliers of cytarabine and daunorubicin HCl (i.e., from (b) (4) or (b) (4) and (b) (4) to (b) (4) and (b) (4) respectively), API comparability studies were performed. Quality data were submitted for two PPQ Batches (6K001 and 7C002) produced using API from (b) (4) (cytarabine) and (b) (4) (daunorubicin). Per the Applicant, PPQ Batch #3 (6K001) conformed to the final proposed IVR acceptance criteria and other Finished Drug Product QC Specifications, but was out-of-specification (OOS) for mean liposome particle size distribution and DSPC content. On the other hand, it was reported that PPQ Batch #4 (7C002, manufactured with the (b) (4) conformed to all proposed Finished Drug Product Specifications. Figure 6 compares the *in vitro* dissolution profiles of PPQ Batch # 7C002 and a pivotal Phase 3 clinical trial batch (4D007) using the proposed QC ((b) (4)-hour) IVR method; the Reviewer's calculated cytarabine and daunorubicin IVR profile similarity factors ($f_2 > 50$) suggest comparable drug release rates.

NOTE: The APIs (daunorubicin and cytarabine) of the to-be-marketed liposomal drug product (VYXEOS®) are the same as the APIs in the FDA approved and US marketed non-liposomal drug products that were used in the Pivotal Phase 3 clinical trials of VYXEOS.

Figure 6. Comparative *in vitro* cytarabine and daunorubicin release profiles of the Process Validation Batch (PPQ Batch #4; 7C002) produced using the APIs from the proposed commercial suppliers vs. the Pivotal Phase 3 Clinical Trial Batches produced using the APIs from the original suppliers (generated at the time of their batch release)



The Reviewer's calculated profile similarity (f_2) values of the process validation batch (7C002) manufactured using the (b) (4) and the APIs from the proposed commercial suppliers *versus* the pivotal Phase 3 clinical trial batches (1E003 and 4D007) were > 50 for both APIs, suggesting similarity of drug release rates between test and reference drug products.

List of Deficiencies:

None

Primary Biopharmaceutics Reviewer Name and Date: Gerlie Gieser, PhD (7/5/2017)

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Okpo Eradiri, PhD (7/11/2017)

Gerlie Gieser

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Ben Stevens

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MICROBIOLOGY

Product Background:

NDA: 209401

Drug Product Name / Strength: Vyxeos (100 mg Cytarabine and 44 mg Daunorubicin) Liposome for Injection

Route of Administration: Intravenous Injection

Applicant Name: Celator Pharmaceuticals, Inc.

Manufacturing Site: (b) (4)

Method of Sterilization: (b) (4)

Review Recommendation: Recommended for approval

Review Summary: The liposome combination drug product is (b) (4) and lyophilized into 50 mL vials.

List Submissions being reviewed: March 31, 2017, May 19, 2017, June 2, 2017 and June 15, 2017.

Highlight Key Outstanding Issues from Last Cycle: None.

Concise Description Outstanding Issues Remaining: None.

Supporting/Related Documents:

DMF (b) (4) (type V)- (b) (4) mic31.doc, dated Aug. 25, 2015, by (b) (4). (b) (4) (adequate)

Remarks Section: Expedited review granted

S Drug Substance

Since the drug product is sterilized during the drug product manufacturing process, then the drug substance will not be reviewed.

P.1 Description of the Composition of the Drug Product

- Description of drug product: The drug product is a lyophilized formulation of cytarabine and daunorubicin in 5:1 molar ratio in a 50 mL vials, that when reconstituted with 19 mL sterile water for injection is a purple colloidal dispersion of liposomes.

- Drug product composition:

Ingredient	Content per mL (after reconstitution)
Cytarabine, USP	5.0 mg
Daunorubicin HCl, USP	2.2 mg
Distearoylphosphatidylcholine (DSPC)	22.7 mg
Distearoylphosphatidylglycerol (DSPG)	6.6 mg
Cholesterol HP, NF	1.6 mg
Copper gluconate, USP	5.0 mg
Triethanolamine (TEA), NF	0.2 mg
Sucrose, NF	102.7 mg
(b) (4)	(b) (4)

- Description of container closure system:

Component	Description	Manufacturer
Vial	50 mL (b) (4) colorless glass vial	(b) (4)
Stopper	(b) (4)	(b) (4)
Cap	20 mm aluminum seal with gray (b) (4) flip-off cap	

Reviewer's Assessment: Acceptable
The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

P.2.5 Microbiological Attributes

Container/Closure and Package Integrity

(3.2.P.2 3.2.P.2.5 Microbiological Attributes)

The applicant indicates that each batch placed on stability will also be tested for container closure integrity following the method described in this section. Twenty vials are immersed in 3M Iron-3 liquid tracer solution, then a – 0.27 ± 0.05 bar vacuum is applied for 10 minutes, then the pressure is brought back to atmospheric over 30 minutes. The vials are removed and rinsed with water then the contents are reconstituted with 19 mL purified water. A 1:16 dilution is then prepared with purified water and the presence of Iron-3 is detected using Quantofix® 100 total

Iron indicator strips, by dipping a strip into each sample, removing the excess solution and reading the color after 5 minutes. A positive Iron-3 measurement is indicated by a blue-violet strip color. One positive control was prepared by adding 2.01 mL of 0.03 M Iron-3 tracer solution and then adding 16.99 mL of purified water to compare to the test samples. In each test a breach positive control is prepared by inserting 0.25 mm diameter fishing line into the vial and resealing with the stopper. A negative control is prepared by reconstituting a drug vial with 19 mL purified water and using a further dilution of 1:16 in the strip test. The applicant provided results for twenty vials from three lots sampled at the beginning, middle and end of the fill, resulting in a total of 140 test samples tested which were all negative for Iron-3, the positive controls were positive.

The applicant conducted a limit of detection study. The limit of detection is (b) (4) mg/L of Iron-3, which the applicant calculated would be equivalent to (b) (4) µL of the 3 M Irion tracer solution per mL of non-diluted sample. To test the minimum breach size detected, the applicant inserted capillaries of 5, 10, 20, and 30 µm into the stoppers of three vials and followed the method outlined above. All but the 10 µm capillary test vials were visually positive for Iron-3 prior to the strip test. Similarly only the 10 µm capillary inserted samples tested negative in the strip test, whereas the 20 and 30 mm samples were observed with an intense color reaction. The Nylon breach sample prepared as indicated in the method above also had an intense color reaction. Thus the applicant concludes that the limit of detection is a (b) (4) µm breach.

Reviewer's Assessment: Acceptable
The applicant provided an acceptable description of the container closure integrity test. The limit of detection study had an unusual result where the 5, 20, and 30 µm capillary samples were positive and the 10 µm capillary was negative. The Agency does not currently provide guidance on an acceptable minimum breach size, however the (b) (4) µL sensitivity of the method is acceptable and within the expected sensitivity of 1-5 µL.

Antimicrobial Effectiveness Testing
The drug product is single-use, AET is not required

Reviewer's Assessment: N/A

P.3 Manufacture

P.3.1 Manufacturers

Drug product:

(b) (4)

P. 3.3 Description of the Manufacturing Process and Process Controls

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Jessica Chiaruttini

Digitally signed by Jessica Chiaruttini
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