CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209347Orig1s000

PRODUCT QUALITY REVIEW(S)

LABELING

{For NDA only}

R Regional Information

1.14 Labeling

Immediate Container Label

(b) (4)

Exela's Previous Proposed Bag Label

(b) (4)

Changes between labels

1. Uncapitalized the active and inactives and removed USP and NF.
2. Revised Storage statement to read as "Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].
3. Added LLC, USA after Exela Pharma Sciences

Reviewer's Assessment: Adequate

IR (1/23/17)

1) Un-capitalize the first letter of each component and delete "USP" and "NF" for each component (active and inactives)

2) Revise storage to: Store at 20-25°C (68°-77°F)

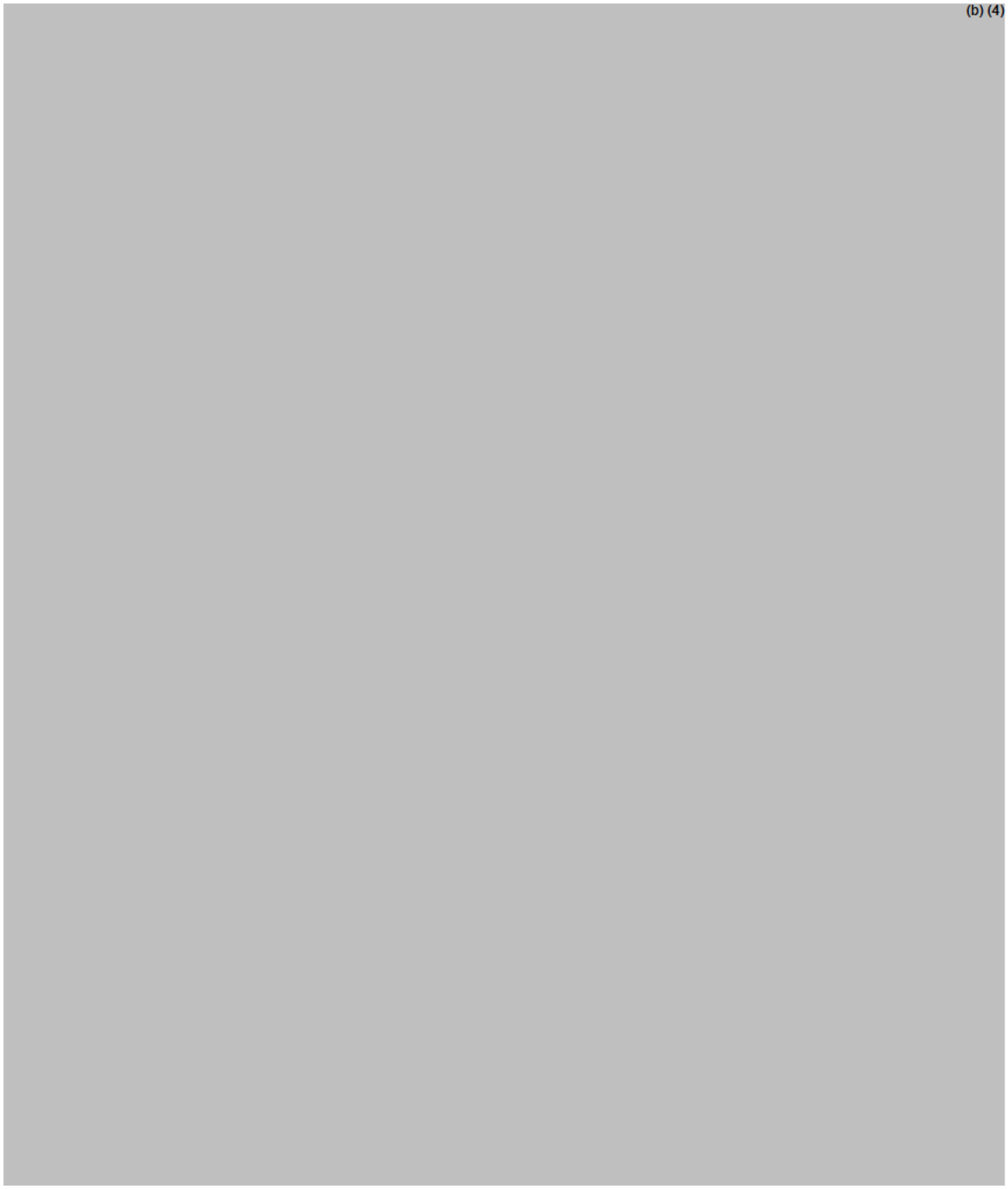
Review Evaluation of the Response

The response of IR (1/23/17) regarding the immediate container labeling has been evaluated and is acceptable. An additional minor change was made to include "LLC, USA" and added as shown above. The additional revision proposed to the immediate container label is acceptable.

Carton Labeling (Secondary Overwrap Labeling)

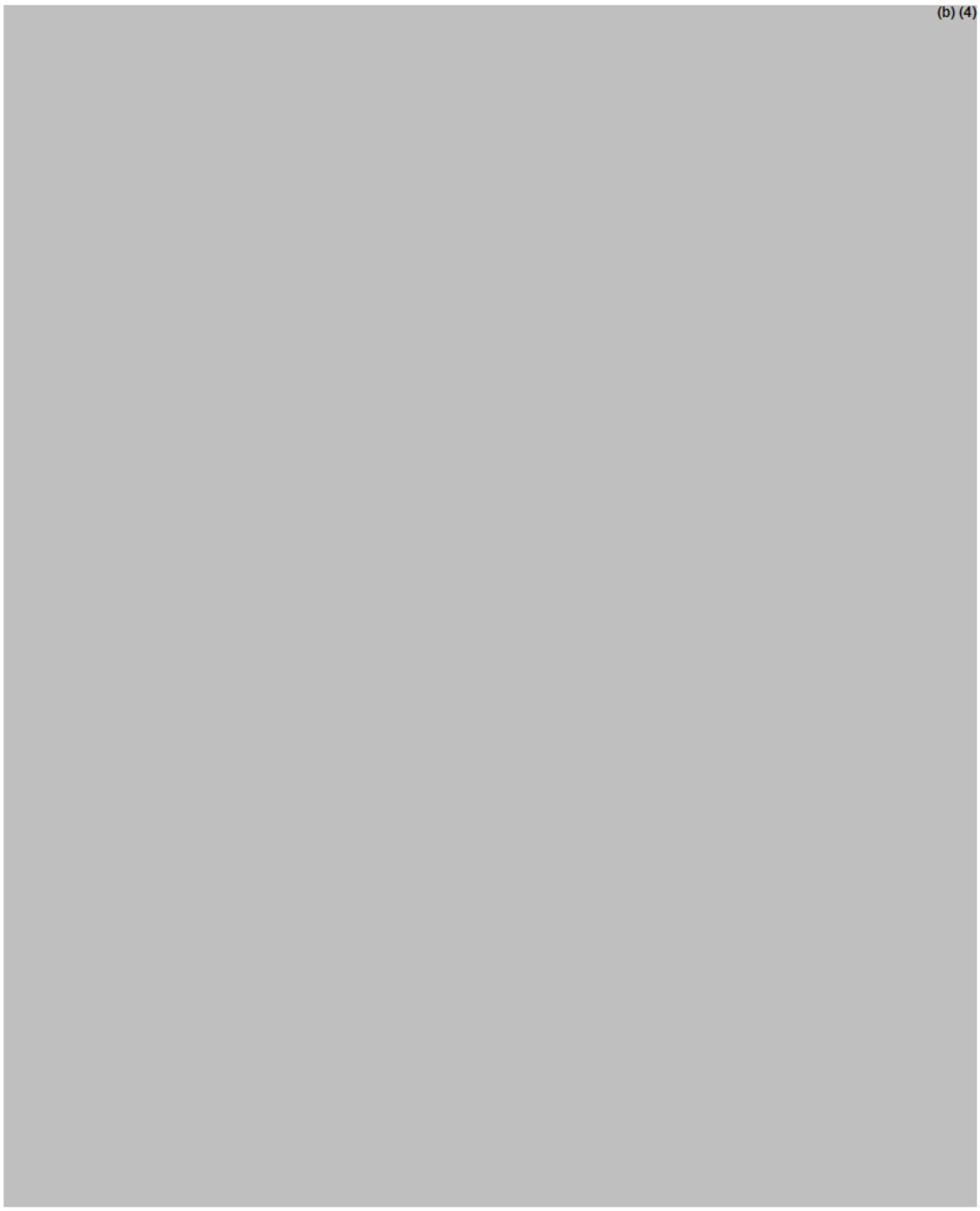
Exela's Revised Proposed Overwrap Label

(b) (4)



Exela's Previous Proposed Overwrap Label

(b) (4)



Changes between labels

1. Uncapitalized the active and inactives and removed USP and NF.
2. Revised Storage statement to read as "Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].
3. Added "Nonpyrogenic" to end of "Sterile, Unpresreved" statement.

4. Spelled out Manufacted and Distributed by statement, added "LLC.," after company name and added city, state, zip code and country.

Reviewer's Assessment: Adequate

IR (1/23/17)
1) Un-capitalize the first letter of each component and delete "USP" and "NF" for each component (active and inactives)

2) Revise storage to: Store at 20-25°C (68°-77°F)

Review Evaluation of the Response
The response of IR (1/23/17) regarding the carton (overwrap) and immediate container labeling has been evaluated is acceptable. Two additional minor changes were made to include "nonpyrogenic" and complete address were added as shown above. The additional revisions proposed to the overwrap are acceptable.

List of Deficiencies:

None

Primary Labeling Reviewer Name and Date:

Milton. J. Sloan, PhD,
Sr. Chemistry Reviewer
OPQ/ONDP/Div1/Branch III
1/24/2016

Secondary Reviewer Name and Date:

Balajee Shanmugam, PhD
(Acting) Branch Chief
OPQ/ONDP/Div1/Branch III
1/24/2016

Balajee Shanmugam

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Milton Sloan

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Recommendation: Approval

NDA 209347
Review 1

Drug Name/Dosage Form	Ganciclovir Injection
Strength	500mg/250mL
Route of Administration	Intravenous Injection (infusion)
Rx/OTC Dispensed	Rx
Applicant	Exela Pharma Sciences
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	18-APR-2016	Original NDA
Amendment	10-JUN-2016	Quality Amendment
Amendment	01-AUG-2016	Quality Amendment
Amendment	08-SEP-2016	Quality Amendment
Amendment	15-DEC-2016	Quality Amendment/Response to IR
Amendment	20-DEC-2016	Amendment/Labeling
Amendment	28-DEC-2016	Quality Amendment/Response to IR

Quality Review Team

DISCIPLINE	REVIEWER	SECONDARY REVIEWER
Drug Substance	Haripada Sarkar	Ali Al Hakim
Drug Product	Milton Sloan	Balajee Shanmugam
Process	Sung Kim	Maotang Zhou
Microbiology	Bernard Marasa	Neal Sweeney
Facility	Cassandra Abellard	Derek Smith
Biopharmaceutics	Mei Ou	Elsbeth Chikhale
Regulatory Business Process Manager	Bamidele (Florence) Aisida	
Application Technical Lead	Stephen Miller	

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	Dec 22, 2016 H. Sarkar	Adequate
	Type II			Adequate	Dec 22, 2016 H. Sarkar	Adequate
	Type III			Adequate	Feb 5. 2-15 A. Shaw	See also the Nov 2016 DP Review of NDA (b) (4) and information in DP review of NDA 209347

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA		

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH	NA			
Clinical	NA			
Other				

Executive Summary

I. Recommendations and Conclusion on Approvability

This NDA is recommended for approval from the Product Quality perspective.

Labeling negotiations are on-going, and product quality recommendations have been conveyed to the full CDER review team. Once labeling is finalized, an amended individual review chapter will be completed to capture the final prescribing information and container labels.

II. Summary of Quality Assessments

A. Product Overview

Ganciclovir Injection, 500 mg/250 mL (2 mg/mL), is indicated for the treatment of CMV retinitis in immunocompromised patients, including patients with acquired immunodeficiency syndrome (AIDS). Ganciclovir Injection is also indicated for the prevention of CMV disease in transplant recipients at risk for CMV disease.

The Listed Drug (LD) product for this 505(b)(2) application is Cytovene® (ganciclovir sodium for injection, 500 mg/vial), which was approved under NDA 019661 on June 23, 1989. The LD required reconstitution of the lyophilized powder with water , followed by dilution with one of four acceptable buffers to give the solution for infusion (typically 100 mL; 10mg/mL or less recommended) that is administered over 1 hour. In addition to the LD, and several related ANDA products, there is a ganciclovir sodium injection (50 mg/mL; 10 mL fill) approved under ANDA 202624.

The Ganciclovir Injection under NDA 209347 is a sterile solution that is intended for direct intravenous injection without further dilution.

Proposed Indication(s) including Intended Patient Population	*Treatment of CMV retinitis in immunocompromised patients, or prevention of CMV disease in transplant recipients at risk for CMV disease.*
Duration of Treatment	*Approximately 134 days*
Maximum Daily Dose	***CMV Treatment*** *Induction: 5 mg/kg (given intravenously at a constant rate over 1 hour) every 12 hours for 14 to 21 days.* *Maintenance: 5 mg/kg (given intravenously at a constant rate over 1 hour) once daily for 7 days* ***per***

	week, or 6 mg/kg once daily for 5 days per week. ***CMV Prevention*** *Induction: 5 mg/kg (given intravenously at a constant rate over 1 hour) every 12 hours for 7 to 14 days.* *Maintenance: 5 mg/kg (given intravenously at a constant rate over 1 hour) once daily for 7 days per week, or 6 mg/kg once daily for 5 days per week until 100 to 120 days post-transplantation.*
Alternative Methods of Administration	*None*

B. Quality Assessment Overview

The drug substance used to manufacture this product is Ganciclovir, USP, which is sourced from by (b) (4)
Both the DMFs were previously reviewed for ANDAs, and were found to be adequate. The subsequent amendments for both the DMFs were reviewed in support of NDA 209-347 and found to be Adequate. See Dr. Sarkar's Drug Substance review for additional information.

Exela's Ganciclovir Injection is a sterile, colorless solution with a concentration of 2 mg/mL ganciclovir in a 250 mL single-dose bags for intravenous use. Each intravenous bag contains 500 mg of ganciclovir, USP in 0.8% sodium chloride. It is intended for direct intravenous infusion without further dilution, and contains sodium chloride (b) (4) and sodium hydroxide and/or hydrochloric acid to adjust the drug product solution to a target pH of 7.5 (b) (4). Exela's formulation contains no preservatives (b) (4) It is packaged in a 250 mL (b) (4) bag from (b) (4) sealed with a Twist off port from Technoflex, and oversealed in an aluminum pouch. The bag is fabricated from (b) (4) layer film designed for (b) (4) medical use (complies with FDA, 21 CFR 177.1810 (b) (3) and USP class VI). The secondary packaging is designed largely to protect the primary package during handling (b) (4). The three NDA registration lots were made at a (b) (4) scale, with the proposed commercial scale of (b) (4) The product shows little or no change over 18 months at the long-term stability condition of 25°C/40%RH or over 6 months at accelerated conditions (40°C/25%RH), which supports a 24 month expiry when stored at USP Controlled Room Temperature. See Dr. Milton Sloan's Drug Product review (including evaluation of labeling) for additional details.

The manufacturing process for the drug product consists of [redacted] (b) (4)

[redacted] (b) (4)

From the Biopharmaceutics perspective, a bridge between the proposed drug product and the LD product has been established in accordance with 21 CFR 320.24(b)(6) regulation. This was based on the applicant's supportive information demonstrating that the physiochemical characteristics (i.e. pH and osmolality) of infusion solution of the proposed drug product is comparable to the reconstituted/diluted LD product, and that the differences in concentration of the active ingredient, administered volume, and infusion rate between the proposed and the LD product will not cause different in the in vivo performance. See Dr. Mei Ou's Biopharmaceutics review for additional details.

Review of the application and inspectional documents of the facilities responsible for manufacturing Ganciclovir Injection per NDA 209347 has determined that there are no significant outstanding risks for these facilities. All facilities were found to be acceptable with no pre-approval inspections required. An Overall Manufacturing Facility Status recommendation of Approve was entered on Oct 31, 2016. See Cassandra Abellard's Facility review for additional details.

C. Special Product Quality Labeling Recommendations

Already conveyed to full CDER review team, as noted above.

D. Final Risk Assessment (see Attachment)

Stephen Miller

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ATTACHMENT I: Final Risk Assessments

Final Risk Table for Ganciclovir Injection (NDA 209347)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Eval.**	**Lifecycle Considerations/ Comments**
Sterility		H	Bioburden reduction by (b) (4) [redacted] suitability of container demonstrated by microbial ingress testing; monitoring sterility on DP specification.	L	
Endotoxins		M	Endotoin monitoring in DS and DP specification with appropriate (b) (4) [redacted] (b) (4)	L	
Assay, Stability		L		L	
Assay (Preservative or Ant-oxidant)	No preservative or anti-oxidant	NA		NA	
Physical Stability (solid-state)		L		L	
Uniformity (Fill/Deliverable Vol		L		L	
Osmolality		L		L	
pH		L		L	
Particulate Matter		M	(b) (4) [redacted] test and acceptance criteria in DP specification	L	
Leachable Extractables		L	Data on DP (Dec 28, 2016 amendment to NDA); data on packaging (DMF (b) (4))	L	
Color Turbidity		L		L	
Water Loss		M	Aluminum overwrap; instructions in PI to keep in overwrap until used	L	

ATTACHMENT II: List of Deficiencies for Complete Response

Responses have been received to all Information Requests, and there are no remaining deficiencies from the Product Quality perspective.

OVERALL ASSESSMENT AND SIGNATURES:

From the Product Quality perspective NDA 209347 is recommended for Approval.

Stephen Miller, Ph.D.; CMC-Lead and ATL for NDA 209347

Stephen Miller

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MICROBIOLOGY

Product Background:

NDA: 209347

Drug Product Name / Strength: (b) (4) (ganciclovir sodium for injection) 2.0 mg/mL

Route of Administration: IV

Applicant Name: Exela Pharma Sciences, LLC.
P.O. Box 818, 1245 Blowing Rock Blvd.
Lenoir, NC 28645

Manufacturing Site:
Exela Pharma Sciences ("Exela")
(Registration Number 3008563008)
1325 William White Place
Lenoir, NC 28645.

Method of Sterilization: (b) (4)

Review Summary: *The submission is* ***recommended*** *for approval on the basis of sterility assurance.*

List Submissions being reviewed (table):

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
04/18/2016	04/18/2016	N/A	05/18/2016
09/08/2016	09/08/2016	N/A	N/A

Highlight Key Outstanding Issues from Last Cycle: None

Concise Description Outstanding Issues Remaining: None. Applicant responded to Agency's Information Request dated 09/02/2016 with Response to Information Request dated 09/08/2016 which was reviewed and found acceptable.

P.1 Description of the Composition of the Drug Product

- **Description of drug product –**
  Ganciclovir Injection is a sterile, unpreserved, single dose, injectable solution for intravenous administration.

- **Drug product composition –**

-

Component	Quality Standard	Function	Ganciclovir Injection 2.0 mg/mL
Ganciclovir	USP	Drug Substance	2.0 mg/mL
Sodium Chloride	USP	(b) (4)	8.0 mg/mL
Sodium Hydroxide, NF (if required)	NF		q.s. to pH 7.5
Hydrochloric Acid, NF (if required)	NF		q.s. to pH 7.5
Water for Injection	USP		(b) (4)

Reviewer's Assessment: Acceptable

P.2 Pharmaceutical Development

- **Description of container closure system –**

Configuration	Component	Description	Manufacturer
2.0 mg/mL 250 mL fill	Bags	250 mL propylene bags	(b) (4) DMF # (b) (4) (b) (4)
	Twist-Offs:	(b) (4) Technoflex Twist-Off	
	Overwrap	Aluminum Overwrap pouches	

Note to Reviewer: (b) (4)

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Neal Sweeney

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Bernard Marasa

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BIOPHARMACEUTICS

Product Background: The Applicant submitted this **NDA 209347** on 04/19/2016. The proposed drug product, Ganciclovir Injection, 2.0 mg/mL, 500 mg/250 mL, is indicated for the treatment of CMV retinitis in immunocompromised patients, including patients with acquired immunodeficiency syndrome (AIDS). Ganciclovir Injection is also indicated for the prevention of CMV disease in transplant recipients at risk for CMV disease.

The Listed Drug (LD) product for this 505(b)(2) application is CYTOVENE® (ganciclovir sodium for injection, 500 mg/vial), which was approved under NDA 019661 on June 23, 1989.

NDA: 209347

Drug Product Name / Strength: Ganciclovir Injection, 2.0 mg/mL, 500 mg/250 mL

Route of Administration: Intravenous Infusion

Applicant Name: EXELA PHARMA SCIENCES LLC

Review Summary: **ADEQUATE**

List Submissions being reviewed (table):

04/19/2016	Original submission
08/01/2016	Response to Biopharmaceutics Information Requests

The Applicant requested a waiver of the requirement to conduct an in vivo bioavailability/bioequivalence study for their proposed drug product based on 21CFR§320.22(b) regulation. The Applicant provided supportive information demonstrating that (a) the physiochemical characteristics (i.e. pH and osmolality) of the reconstituted diluted infusion solution of the proposed drug product is comparable to the LD product; (b) the differences in concentration of the active ingredient, administered volume, and infusion rate between the proposed drug product and the LD product do not affect the in vivo bioavailability and bioequivalence.

Upon review of the provided information, from the Biopharmaceutics perspective, we consider that a bridge between the proposed drug product and the LD product has been established in accordance with 21 CFR 320.24(b)(6) regulation.

Overall Comment and Recommendation:

A bridge between the proposed drug product and the LD product has been established. From the Biopharmaceutics perspective, NDA 209347 for Ganciclovir Injection, 2.0 mg/mL, 500 mg/250 mL, is recommended for APPROVAL.

BCS Designation

Reviewer's Assessment:

Solubility: The drug substance, Ganciclovir, is highly soluble in water; freely soluble in 1 N sodium hydroxide; soluble in dimethylsulphoxide; practically insoluble or insoluble in acetone, methanol and dichloromethane (from M.3.2.S.1.3).

Permeability: n/a

Dissolution: n/a

Dissolution Method and Acceptance Criteria

Reviewer's Assessment: n/a

Clinical relevance of dissolution method & acceptance criteria (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)

Reviewer's Assessment: n/a

Application of dissolution/IVIVC in QbD

Reviewer's Assessment: n/a

MODIFIED RELEASE ORAL DRUG PRODUCTS –In-Vitro Alcohol Dose Dumping

Reviewer's Assessment: n/a

In-Vitro Soft-food Interaction Study

Reviewer's Assessment: n/a

In-Vitro Release Testing (IVRT) for Semi-Solid Products

Reviewer's Assessment: n/a

In-Vitro Permeation Testing (IVPT) for Transdermal/Topical Products

Reviewer's Assessment: n/a

In-Vitro Dissolution Testing for Abuse-deterrent Products

Reviewer's Assessment: n/a

In-Vitro BE Evaluation for Pulmonary Products

Reviewer's Assessment: n/a

EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim

Reviewer's Assessment: n/a

Bridging of Formulations

Reviewer's Assessment: As noted in M.2.3.P, the developmental formulation is the same as the commercial formulation, no other formulations were investigated. Therefore, bridging between different formulations used during the development is not needed.

Biowaiver Request

Reviewer's Assessment: ADEQUATE

The proposed drug product is a parenteral drug product intended for administration by intravenous infusion. In M.1.12, the Applicant submitted a "request for waiver for in vivo studies" (biowaiver request) per 21CFR§320.22(b), in order to waive the requirement to conduct in vivo bioavailability/bioequivalency (BA/BE) studies for the proposed drug product, Ganciclovir Injection, 2.0 mg/mL.

The provided supporting information included:

1. The proposed drug product is a parenteral drug product intended for administration by intravenous infusion.
2. The proposed drug product has the same active ingredient, route of administration, and indications as the LD product, CYTOVENE®.
3. The proposed drug product differs from the LD product in active ingredient concentration, the inactive ingredients that may be present, and the dosage form.

The active ingredient of the LD product is 500 mg ganciclovir as the sodium salt (b) (4) sodium) lyophilized powder per vial. Reconstitution of the lyophilized powder with 10 mL of sterile water yields a 50 mg/mL of reconstituted ganciclovir solution with pH 11. The reconstituted solution is further diluted with an appropriate intravenous solution, such as 0.9% sodium chloride, 5% dextrose, ringer's injection, or lactated ringer's injection before infusion.

The proposed drug product formulation contains sodium chloride and water (b) (4) and may contain sodium hydroxide and hydrochloric acid (as pH adjusters) to achieve a target pH 7.5. The proposed drug product formulation contains no preservatives, (b) (4) The proposed drug product is a ready to use injectable solution and requires no reconstitution or dilution prior to intravenous administration.

The component and composition of the LD product and the proposed drug product are given in Table 1a and 1b below.

Table 1a: The component and composition of the LD product and the proposed drug product (from M.1.12)

Exela's Formulation		**Genentech, Inc, CYTOVENE® –IV (ganciclovir sodium for injection) Formulation**[1]	
Ingredients	**Composition**	**Ingredients**	**Composition**
Ganciclovir, USP	2.0 mg/mL 500 mg/250 mL	Ganciclovir (present as sodium salt)	500 mg/vial
Sodium Chloride, USP	8.0 mg/mL (b) (4)	Sodium Chloride, USP	Absent
Sodium Hydroxide, NF (if required)	q.s. to pH 7.5 (b) (4)	Sodium Hydroxide, NF	Equivalent to about (b) (4) upon reconstitution)
Hydrochloric Acid, NF (if required)	q.s. to pH 7.5 (b) (4)	Hydrochloric Acid, NF	Absent
Water for Injection, USP	q.s.	Water for Injection, USP	Absent

Table 1b: The component and composition of the LD product and the proposed drug product (from M.1.12)

	Genentech, Inc, CYTOVENE® –IV (ganciclovir sodium for injection) Formulation (RLD)	**Exela's Ganciclovir Injection**
Strength(s)	500 mg/vial (as Ganciclovir)	2.0 mg/mL
Configurations/ Label Claim	500 mg/vial (as Ganciclovir)	500 mg/250 mL
Active Ingredient	Ganciclovir, USP	Ganciclovir, USP
Excipients	Sodium hydroxide	Sodium hydroxide (if required) Hydrochloric acid (if required) Sodium Chloride
Solvent	Water for Injection (b) (4) (b) (4)	Water for Injection
Dosage Form	Injection, lyophilized powder	Injection, solution
Route of Administration	Intravenous	Intravenous

The list of ingredients, their pharmaceutical functions, and amount per unit basis of the proposed drug product were given in Table 2 below.

Table 2: The list of ingredients, their pharmaceutical functions, and amount per unit basis of the proposed drug product (from M.2.3.P.1)

Component	Quality Standard	Function	Ganciclovir Injection (2 mg/mL, 500 mg/250 mL)
Ganciclovir	USP	Drug Substance	2 mg/mL
Sodium Chloride	USP	(b) (4)	8 mg/mL
Hydrochloric Acid	NF	pH adjuster	pH to 7.5 (b) (4)
Sodium Hydroxide	NF	pH adjuster	pH to 7.5
Water for Injection	USP	(b) (4)	(b) (4)

The excipients used in the proposed drug product were sodium chloride, USP, sodium hydroxide, NF, hydrochloric acid, NF, and water for injection, USP. All applicable excipients in the bulk drug product solution fall below the (b) (4) limits (Table 3).

Table 3: (b) (4) levels of the excipients in the proposed drug product (from M.1.12)

Ingredients	(b) (4) Levels[1]	Concentration % v/v
Sodium Chloride, USP	Intravenous (Infusion); Injection (b) (4)	0.8%
Water for Injection, USP	N/A	(b) (4)

The multiple physicochemical characteristics testing results for drug product release and stability of three stability batches of the proposed drug product were submitted. The pH and osmolality data of these three batches were summarized in Table 4 below.

Table 4: The pH and osmolality of the proposed drug product (from M.3.2.P.5.1 and M.3.2.P.5.4)

	Proposed Specifications	Test Results Batch No. XLNE1411	Test Results Batch No. XLNE1411	Test Results Batch No. XLNE1411
pH	6.5-8.0	7.0	7.5	7.5
Osmolality	240-280 mOsm/kg	257 mOsm/kg	258 mOsm/kg	256 mOsm/kg

Reviewer's assessment:

From the Biopharmaceutics perspective, the comparative testing data showed that the minor difference in pH and osmolality would not affect the in vivo BA/BE behavior of the proposed drug product compared to the LD product.

Therefore, the different excipients (inactive ingredients) are not expected to affect the in vivo BA/BE behavior of the proposed drug product compared to the LD product.

In order to further evaluate the effect of the difference in administered volume and the difference in the active ingredient concentration of the proposed drug product compared to the LD product, one Biopharmaceutics information request (IR) was conveyed to the Applicant. The IR comments and responses are summarized below:

Biopharmaceutics IR comments (conveyed on 07/08/2016):

The submitted biowaiver request is based on 21CFR§320.22(b), however, your proposed drug product (Ganciclovir Injection) does not contain the same concentration of active ingredient and same volume administered compared to the listed drug product (CYTOVENE-IV).

For example, based on the labeling of listed drug product the recommended initial dosage is 5 mg/kg for a 70 kg patient with normal renal function. Based on the labeling, a vial of 500 mg listed drug product will be reconstituted in 10 mL of sterile water to give a 50 mg/mL concentrated solution. (b) (4)

In order to evaluate the biowaiver request, based on 21 CFR 320.24(b)(6), you need to provide the following supporting data/information:

a) Physiochemical characteristics (i.e. pH and osmolality) of the reconstituted diluted infusion solution of the listed drug product compared to your proposed drug product. Justify any differences;

b) Information indicating whether the differences (e.g. worst case scenario) in concentration of the active ingredient, administered volume, and infusion rate between the listed drug product and your proposed drug product do or do not affect the in vivo bioavailability and bioequivalence.

The responses to the above IR comments (received 08/01/2016) are summarized below:

Applicant's response to IR a):

The physiochemical characteristics of the diluted infusion solution of the listed drug product, CYTOVENE®-IV (ganciclovir sodium for injection), 500 mg/vial , NDA 019661, and Exela's proposed drug product, Ganciclovir Injection, 2.0 mg/mL, 500 mg/250mL were evaluated,

specifically, with respect to pH and osmolality. Two vials of the listed drug, CYTOVENE®-IV (ganciclovir sodium for injection), 500 mg/vial, lot number G70752, expiration date 11/2017, were reconstituted with 10 mL of Sterile Water for Injection, USP, (b) (4) Lot Number C993881, expiration date 10/2016, and mixed until complete dissolution was observed. Consistent with the listed product labeling (and consistent with the worst case scenario discussed below for a 100 kg patient), the entire content of one reconstituted vial was admixed with 100 mL of 0.9% Sodium Chloride Injection, USP, (b) (4) Lot Number Y010363, expiration date 04/2017, and 5% Dextrose Injection, USP, (b) (4) Lot Number P321885, expiration date 08/2016 and mixed.

The pH and osmolality of the reconstituted listed drug product, the diluted listed drug product in 0.9% Sodium Chloride Injection and 5% Dextrose Injection, USP, and Exela's proposed drug product, Ganciclovir Injection, 2.0 mg/mL, 500 mg/250mL, NDA submission stability lot number XLNE1412 were measured according to USP <791> and USP <785> respectively. The data is presented in Table 5.

Table 5: Comparison of the Physiochemical Characteristics (pH and osmolality) of the reconstituted listed drug product, the diluted listed drug product in 0.9% Sodium Chloride Injection and 5% Dextrose Injection, USP, and Exela's proposed drug product, Ganciclovir Injection, 2.0 mg/mL, 500 mg/250mL (from 08/01/2016 submission)

	CYTOVENE® - IV (reconstituted)	CYTOVENE® - IV (diluted)		Exela's Proposed Drug Product
		With 0.9% NaCl	With 5% Dextrose	
pH	10.94	10.60	10.15	7.5
Osmolality	316 mOsm/kg	292 mOsm/kg	268 mOsm/kg	258 mOsm/kg

Based on the pH and Osmolality data measured for the reconstituted listed drug product, the diluted reconstituted listed drug product, and Exela's proposed drug product, Ganciclovir Injection, 2.0 mg/mL, 500 mg/250mL, NDA submission stability lot number XLNE1412, as shown in Table 5, there are noted differences between the listed drug product and Exela's drug product. These differences are discussed in detail below.

pH

The current listed drug labeling contains the following warning:

Caution should be exercised in the handling and preparation of solutions of CYTOVENE-IV. Solutions of CYTOVENE-IV are alkaline (pH 11). Avoid direct contact of the skin or mucous membranes with CYTOVENE-IV solutions.

In addition:

(b) (4)

(b) (4)

One of the objectives of Exela's reformulation efforts was to reduce the pH of the product to eliminate or minimize the hazards associated with CYTOVENE's high pH. (b) (4)

Such reactions include phlebitis and/or pain at the site of infusion. The CYTOVENE labeling recommends that the infusion should be administered only into veins with adequate blood flow to permit rapid dilution and distribution.

Exela's proposed drug product is designed to overcome the above pH-related issues. This objective was achieved first by selecting a non-sodium salt drug substance (e.g., ganciclovir itself) which allowed lowering the pH to a pH that is closer to the physiological pH. This lowered pH minimizes or eliminates the site reaction hazard and consequently, the administrator may not need to rely on selecting a suitable location for infusion (even though still may be desirable) to accomplish "rapid dilution and distribution" in vivo. Secondly, because Exela's proposed drug product is provided in a pre-mixed form, there is no need for any aseptic handling by pharmacy personnel, thereby eliminating potential for the hazard related to the handling of the product mentioned in the CYTOVENE's labeling, contamination, medication errors, and the attendant time and expense to health systems. Thus, Exela's proposed drug product's pH change and its premixed formulation results in a safe and effective ganciclovir product.

Osmolality

The osmolality of Exela's proposed drug product is about 258 mOsm/kg, thus is considered slightly hypotonic. The listed drug product, as per the current labeling, can be diluted following reconstitution with 10 mL of Water for Injection, USP, with 0.9% Sodium Chloride, 5% Dextrose, Ringer's Injection, and Lactated Ringer's Injection, USP. The reconstituted listed drug product and the diluted listed drug product (in 0.9% Sodium Chloride Injection) have an osmolality of about 316 mOsm/kg and about 292 mOsm/kg respectively. If the listed drug product is diluted with 5% Dextrose per the current labeling, the osmolality, about 268 mOsm/kg, is similar to that of Exela's proposed drug product, about 258 mOsm/kg. In addition, D5W (5% Dextrose Injection) is infused with an osmolality of around 250 mOs/kg in high volumes with no apparent safety concerns. The osmolality data are excerpted as below (Table 6) for a commonly used D5W product offered by Baxter Pharmaceuticals, NDA 016694.

Table 6: Physiochemical Characteristics (pH and osmolality) of a D5W Product (from 08/01/2016 submission)

	Size (mL)	*Dextrose Hydrous, USP (g/L)	Osmolarity (mOsmol/L) (calc.)	pH nominal (range)	Caloric Content (kcal/L)
5% Dextrose Injection, USP	250 500 1000	50	252	4.5 (b) (4)	170

Additional products that are even more hypotonic are provided in the Table 7 below:

Table 7: Osmolality of Few Approved Hypotonic Products (from 08/01/2016 submission)

Product	NDA/ANDA	Osmolality (mOsm/kg)
Potassium Chloride 20mEq/mL in ½ NS	ANDA078446[2]	194
Sodium Chloride 0.45%	NDA018016[3]	154

Thus, it is submitted that the osmolality of Exela's proposed drug product poses no safety concern.

Applicant's response to IR b):

Taking a 100 kg body weight patient as a reasonable worst case scenario, the relevant data on concentration of the active ingredient, administered volume, and infusion rate of the fully diluted listed drug product and Exela's proposed drug product are provided in Table 8 below.

Table 8: Comparative data for administration conditions (from 08/01/2016 submission)

	CYTOVENE® - IV (diluted)	Exela's Proposed Drug Product
Ganciclovir (total dose)	500 mg	500 mg
Administered volume[4]	110 mL (10 mL + 100 mL)	250 mL
Concentration of the active ingredient (Ganciclovir)	4.55 mg/mL	2.0 mg/mL
Infusion rate (volume of fluid)	110 mL/1 hr = 1.83 mL/min	250mL/1 hr = 4.17 mL/min
Infusion rate (mg of Ganciclovir)	8.33 mg/min	8.33 mg/min

As shown in Table 8, the concentration of Ganciclovir in the diluted listed drug product (4.55 mg/mL), and Exela's proposed drug product (2.0 mg/mL), are different. However, Exela's proposed drug product is designed to provide the same total amount of Ganciclovir per dose (i.e., 5 mg/kg or 500 mg for a 100 kg patient) and at the same rate (i.e., 8.33 mg/min) as the listed

drug. This objective is achieved by increasing the rate of infusion fluid from a constant rate of 1.83 mL/min (for the listed drug) to a constant rate of 4.17 mL/min (for Exela's proposed drug product). As discussed below, this increased rate of fluid administration and the increased volume of fluid administered from Exela's proposed drug product have no practical impact on the pharmacokinetics of the drug, and may even confer some advantages to Exela's proposed drug product.

The steady state volume of distribution of Ganciclovir following intravenous administration is reported to be 0.74 ± 0.15 L/kg (n=98) in CYTOVENE® - IV labeling. For a 100 kg patient, this represents approximately 74.0 ± 15 L. Infusion of an additional 140 mL (250 mL-110 mL) to a 100 kg patient from Exela's proposed drug product results in an estimate of 0.14L/(74-15)L = 0.0020 or a 0.20% increase in the volume of distribution. As a conservative estimate, using the volume of central compartment (46 ± 14 L) as the volume of distribution, infusion of an additional 140 mL (250 mL-110 mL) to a 100 kg patient from Exela's proposed drug product results in an estimate of 0.14L/(46-14)L = 0.0044 or a 0.44% increase in the volume of distribution, which is insignificant. Therefore, the additional volume of fluid administered with Exela's proposed drug product is not expected to materially change the peak (Cmax) and trough (Cmin) concentrations of Ganciclovir.

Studies have shown that following infusion of 2 L of normal saline, 60% of the fluid remained in the body after 6 hours and therefore does not significantly increase diuresis.6 Thus, the additional volume (150 mL) administered during infusion of Exela's proposed drug product, at the worst case scenario (100 kg patient) is not likely to increase diuresis.

Cytovene labeling provides the following with respect to elimination of Ganciclovir:

When administered intravenously, ganciclovir exhibits linear pharmacokinetics over the range of 1.6 to 5.0 mg/kg and when administered orally, it exhibits linear kinetics up to a total daily dose of 4 g/day. Renal excretion of unchanged drug by glomerular filtration and active tubular secretion is the major route of elimination of ganciclovir. In patients with normal renal function, 91.3 ± 5.0% (n=4) of intravenously administered ganciclovir was recovered unmetabolized in the urine. Systemic clearance of intravenously administered ganciclovir was 3.52 ± 0.80 mL/min/kg (n=98) while renal clearance was 3.20 ± 0.80 mL/min/kg (n=47), accounting for 91 ± 11% of the systemic clearance (n=47). Half-life was 3.5 ± 0.9 hours (n=98) following IV administration and 4.8 ± 0.9 hours (n=39) following oral administration.

Renal clearance of unchanged drug is the major elimination route and accounts of about 90% total clearance of Ganciclovir. As noted above, because the additional 140 mL of fluid from Exela's proposed drug product does not cause diuresis, it has no meaningful impact on the elimination of Ganciclovir. Further, because the additional 140 mL of fluid has a negligible effect on Ganciclovir volume of distribution (about 0.4% - using volume of central compartment), the pharmacokinetics (i.e., Cmax, AUC, and elimination rates) of Ganciclovir are expected to remain essentially unchanged. Finally, because Ganciclovir displays linear kinetics over a wide range of dosing from 1.6 to 5.0 mg/kg, which is the dosing range for Exela's proposed drug product, the efficacy or safety of Ganciclovir will remain unchanged compared to the listed drug.

On the other hand, the additional fluid provided by Exela's proposed drug product is consistent with the recommendation in the listed product labeling which states that "Administration of CYTOVENE-IV solution should be accompanied by adequate hydration". The labeling does not elaborate on what "adequate hydration" is. However, the label for Cidofovir (VISTIDE), which has the same indication and belongs to the same class of compounds, defines hydration as follows:

"Patients must receive at least 1 L of 0.9% (normal) saline solution intravenously with each infusion of VISTIDE. The saline solution should be infused over a 1-2 hour period immediately before the VISTIDE infusion. Patients who can tolerate the additional fluid load should receive a second liter. If administered, the second liter of saline should be initiated at the start of the VISTIDE infusion or immediately afterwards, and infused over a 1 to 3 hour period."

Based on the above recommendations for hydration, the rate of infusion for normal saline or fluid input via the intravenous route in this patient population could be as high as 16.7 mL/min (1000 mL/60 min) or as low as 5.56 mL/min (1000 mL/180 min). As shown in Table 8, the rate of infusion of Exela's proposed drug product will be 4.17 mL/min, which is far below 16.7 mL/min and below the recommended low infusion rate of 5.56 mL/min. Also, the additional volume administered with Exela's product (140 mL) is far below the recommended hydration protocol volume of 1 to 2 L. Therefore, the rate of administration and the volume of administration for Exela's proposed drug product are not expected to cause any adverse effects in the relevant patient population.

Finally, the listed product is not restricted to an infusion fluid volume of 100 mL only. CYTOVENE® - IV labeling provides the following with respect to Infusion Solution:

"Based on patient weight, the appropriate volume of the reconstituted solution (ganciclovir concentration 50 mg/mL) should be removed from the vial and added to an acceptable infusion fluid (typically 100 mL) for delivery over the course of 1 hour. Infusion concentrations greater than 10 mg/mL are not recommended".

Medication fact sheet for CYTOVENE® - IV states:

"Each dose of Ganciclovir is put in 100 or 250 mL bags."10 If the listed product is indeed added to a 250 mL bag, the infused volume will be 260 mL and the concentration of Ganciclovir will be as low as 500 mg/260 mL = 1.92 mg/mL. These figures are closer to those of Exela's proposed drug product. Consequently, the rate of administration of the listed product (4.33 mL/min) is also closer to that of Exela's proposed drug product (4.17 mL/min).

In conclusion, the small increase in the volume administered (140 mL) with Exela's proposed drug product compared to the diluted reconstituted listed drug product (typical 110 mL) is not likely to negatively impact the safety of Ganciclovir. In contrast, the pH of Exela's proposed drug product (about 7.5) is closer to physiological pH (about 7.4). Therefore, Exela's proposed drug product should be considered at least as safe as the listed product, if not safer.

Reviewer's assessment of the Applicant response (dated 08/01/2016) to the Biopharmaceutics Information Request (dated 07/08/2016):

Because the proposed drug product, Ganciclovir Injection, 2.0 mg/mL, has different inactive ingredients and a different dosage form compared to the LD product, 21CFR§320.22(b) was not an appropriate regulation for a biowaiver request, which requires the proposed drug product and the LD product should contain the same active and inactive ingredients in the same concentration.

*However, the overall provided responses and justifications are considered adequate. The Applicant provided the supportive information demonstrating that the differences in concentration of the active ingredient, administered volume, and infusion rate between the proposed and the LD product will not cause different in the in vivo performance. Upon review of the above information, based on the 21 CFR 320.24(b)(6) regulation, from the Biopharmaceutics perspective, we consider that a bridge between the proposed drug product and the LD product has been established. Therefore, from the Biopharmaceutics perspective, NDA 209347 for Ganciclovir Injection, 2.0 mg/mL, 500 mg/250 mL, is recommended for **APPROVAL**.*

R Regional Information

Comparability Protocols

Reviewer's Assessment: n/a

Post-Approval Commitments

Reviewer's Assessment: n/a

Lifecycle Management Considerations

n/a

List of Deficiencies:

n/a

Primary Biopharmaceutics Reviewer Name and Date:

10/10/2016
Mei Ou, Ph.D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
I concur with Dr. Ou's assessment and recommendation.

10/12/2016
Elsbeth Chikhale, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

Elsbeth Chikhale

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Mei Ou

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