CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209387Orig1s000

CHEMISTRY REVIEW(S)

QUALITY ASSESSMENT

NDA 209387(Sodium Nitroprusside in 0.9% Sodium Chloride Injection) Review

Product Quality Recommendation: Recommended for Approval

Drug Name/Dosage Form	Sodium Nitroprusside in 0.9% Sodium Chloride Injection
Strength	50 mg/100 mL (0.5 mg/mL); single-use vials
Route of Administration	Intravenous Infusion
Applicant	Exela Pharma Sciences, LLC
US agent, if applicable	N/A

Quality Review Team

DISCIPLINE/ROLE	REVIEWER	BRANCH/DIVISION
Drug Substance	Sharon Kelly	ONDP/DNDAPI/NDBI
Drug Product	Rao Kambhampati	ONDP/DNDPI/NDPBI
Process	Kumar Janoria	OPF/DPAIII/PABVII
Microbiology	Yuansha Chen	OPF/DMA/MABIII
Facility	Christina Capacci-Daniel	OPF/DIA/IABII
Biopharmaceutics	Om Anand	ONDP/DB
RBPM	Dahlia A.Woody	OPRO DRBPMI/RBPMBI
Environmental Assessment	Rao Kambhampati	ONDP/DNDPI/NDPBI
Laboratory (OTR)	N/A	N/A
ORA Lead	N/A	N/A
Application Technical Lead (ATL)	Mohan Sapru	ONDP/DNDPI/NDPBI

Submissions (s) Reviewed	NDA 209387, DMFs, and all the submitted CMC amendments

Quality Review Data Sheet

1. **RELATED/SUPPORTING DOCUMENTS:**

DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS
(b) (4)	II	(b) (4)	Drug Substance	Adequate
	II		Drug Substance	Adequate

2. **CONSULTS:**

No consults requested.

Executive Summary (Next Page)

EXECUTIVE SUMMARY

I. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing, and controls (CMC) perspective, NDA 209387 (Sodium Nitroprusside in 0.9% Sodium Chloride Injection) is recommended for approval.

Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: Not applicable

II. SUMMARY OF QUALITY ASSESSMENTS

The applicant, Exela Pharma Sciences, LLC, sought U.S. marketing approval for Sodium Nitroprusside in 0.9% Sodium Chloride Injection under the provisions of Section 505(b)(2) of the Federal Food and Cosmetic Act and 21 CFR §314.54. Hospira's NITROPRESS® (Sodium Nitroprusside Injection) is the referenced listed drug (RLD). The parenteral route of administration of the proposed drug product is the same as that of the RLD. The RLD NITROPRESS® (Sodium Nitroprusside Injection), is not suitable for direct injection because the solution must be further diluted in sterile 5% dextrose injection before infusion. However, Exela's proposed formulation, Sodium Nitroprusside (b) (4) Injection, is intended for direct intravenous infusion without further dilution. The proposed formulation is indicated for the immediate reduction of blood pressure of adult and pediatric patients in hypertensive crisis, and for the treatment of acute (b) (4) heart failure.

A. Drug Substance (Sodium Nitroprusside, USP, as Dihydrate) Quality Summary

The drug substance Sodium Nitroprusside (as dihydrate) is light brown to reddish brown (b) (4) or powder, which is freely soluble in water. Sodium Nitroprusside does not exhibit isoelectric point, chirality, and isomerism. For all CMC details concerning Sodium Nitroprusside, USP, including structural characterization, manufacturing processes, control strategies, and process controls that ensure consistent production of the of the drug substance, the applicant has cross-referenced the (b) (4) As part of NDA review, the type II DMFs (b) (4) were reviewed and found adequate (refer to reviews for DMF (b) (4) and DMF (b) (4) by Dr. S. Kelly, dated 02-12-2017 in DARRTS).

Control Strategy: The applicant has provided release specification, and batch analysis data for the drug substance in the NDA. The proposed specification includes monitoring all critical quality attributes of the drug substance. The levels of identified impurities i.e., (b) (4) are controlled by drug substance specification with acceptance limits of NMT (b) (4) %. Acceptance limits for the residual solvents such as (b) (4) have been established in accordance with the ICH requirements. The bacterial endotoxins specification of NMT (b) (4) EU/mg has been established to ensure that the finished product complies with USP requirements for bacterial endotoxins. The testing procedure is based upon USP<85>. The microbial limits for the drug substance are in agreement with USP requirements, General Chapter USP <61> and <62>. The analytical methods for the analysis of

Sodium Nitroprusside, USP include the compendial testing methods in addition to HPLC assay and residual solvent testing methods, which have been validated by the drug substance suppliers. Method verifications have also been performed by Exela for the applicable compendial methods as well as the methods provided by the drug substance suppliers.

Retest Period and Storage Conditions: Based on adequate stability data, a retest period of (b) (4) has been assigned for Sodium Nitroprusside, USP when stored at (b) (4) °C.

B. Drug Product [Sodium Nitroprusside in 0.9% Sodium Chloride Injection] Quality Summary

The applicant has proposed a ready-to-use formulation (Sodium Nitroprusside in 0.9% Sodium Chloride Injection) version of the RLD i.e., previously FDA approved Nitropress® (sodium nitroprusside injection). The proposed formulation is a sterile, unpreserved, single dose, solution intended for intravenous infusion without further dilution. Each mL contains 0.5 mg of Sodium Nitroprusside, USP, 9 mg of sodium chloride, USP, in Water for Injection, USP. None of the compendial excipients i.e., sodium chloride, USP, and Water for Injection, USP, used in the manufacture of the drug product, are produced from any materials of human or animal origin. Hence, there is no reason to suspect the presence of Bovine Spongiform Encephalopathy infectious agent in the excipients.

Regarding comparison of Exela's formulation with the Hospira's RLD, the active ingredient concentration of the RLD is 25 mg/mL (50 mg/2 mL) and is diluted with 5% dextrose for injection (DFI) prior to intravenous infusion. The active ingredient concentration in Exela's proposed drug product is 0.5 mg/mL (50 mg/100 mL). The RLD product contains only Water for Injection, USP (b) (4) whereas, Exela's proposed formulation contains Sodium chloride, USP as a (b) (4) agent, and Water for Injection, USP (b) (4). While the above differences with respect to active ingredient concentration and inactive ingredients present are significant from a formulation perspective, they are not expected to affect the safety or efficacy of Exela's proposed drug product formulation.

Regarding the total sodium content of the proposed formulation, each vial (100 mL) of the proposed drug product solution contains a total of (b) (4) mg of total sodium ((b) (4) mg of sodium is from Sodium Nitroprusside API and (b) (4) mg of sodium is contributed by sodium chloride excipient. Therefore, each 1 mL of the drug product solution contains (b) (4) mg of total sodium. Based on assessment of clinical implications, the clinical review team found the total sodium content in the formulation acceptable.

Manufacturing: The drug product is manufactured by (b) (4) (b) (4)

(b) (4)

Control Strategy: The product control strategy mainly consists (b) (4) . The specifications for the excipients are based on the specifications established in the USP and/or NF. The product release specification includes tests for all the identified drug product critical quality attributes (CQAs). The identity of the drug substance is confirmed using a (b) (4) techniques. No degradation products have been found in the drug product lots at release or during stability studies. The proposed limits for individual unspecified impurities are set in accordance with ICH Q3 (B) requirements and the available accelerated and real time stability data. The proposed pH range (b) (4) and osmolality (270-310 mOsm/kg) are physiologically compatible. The sterility assurance validations supporting the proposed formulation are acceptable. The bacterial endotoxin specification has been established at (b) (4) EU/mL (equivalent to NMT (b) (4) EU/mg) to ensure that the finished product complies with USP requirements for bacterial endotoxins based on the maximum total daily dose. The proposed tests and acceptance criteria for container closure integrity, sterility, and bacterial endotoxins tests are acceptable. The testing procedure is based upon USP<85>. Compliance with USP <467> (b) (4) All applicable methods have been validated or verified.

Container Closure System: The drug product is filled into amber, USP Type I, molded glass vials, sealed with stoppers and oversealed with aluminum Flip-Off overseals from (b) (4) The proposed container and closure system is commonly used in packaging of sterile injection formulations. Health care providers will calculate the required quantity on the basis of the patient's weight, rate of administration, and dose. All results from extractable testing per (b) (4) using (b) (4) as solvent are acceptable. Potential for delamination is minimal because the pH of the solution is (b) (4) and the formulation does not contain a strong base. The container closure system is adequate to protect the drug product from heat, humidity, and microbial contamination. Since the drug product solution is sensitive to light, the amber vial is packaged in a secondary carton.

Expiration Date & Storage Conditions: The proposed product shelf-life of (b) (4) months stored is not adequately supported by product stability data. Based on 12-month long-term and 6-month accelerated stability data, 12 months expiration dating period is appropriate when the drug product is stored at 25^{0}C in the commercial container closure system.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Not finalized at this stage
Non-Proprietary Name of the Drug Product	Sodium Nitroprusside in 0.9% Sodium Chloride Injection
Non Proprietary Name of the Drug Substance	Sodium Nitroprusside, USP, as Dihydrate
Proposed Indication(s) including Intended Patient Population	Sodium Nitroprusside in 0.9% Sodium Chloride Injection is indicated for: • Immediate reduction of blood pressure • Producing controlled hypotension to reduce bleeding during surgery • Treatment of (b) (4) heart failure
Methods of Administration	Intravenous Infusion. Must be delivered by a volumetric infusion pump because small variations in infusion rate can lead to wide, undesirable variations in blood pressure Warning regarding administration of Sodium Nitroprusside in 0.9% Sodium Chloride Injection: Sodium nitroprusside can cause precipitous decreases in blood pressure which can lead to irreversible ischemic injuries or death. Use only with continuous blood pressure monitoring Sodium nitroprusside metabolism produces dose-related cyanide, which can be lethal. A patient's ability to buffer cyanide will be exceeded in less than one hour at the maximum dose rate (10 mcg/kg/min); limit infusion at the maximum rate to as short a duration as possible
Maximum Daily Dose/ Duration of Treatment	The recommendation is to initiate infusion of sodium nitroprusside at a rate of 0.3 mcg/kg/min, and titrate every few minutes until the desired effect is achieved or the maximum recommended infusion rate of 10 mcg/kg/min has been reached

D. Carton label:

(b) (4)

[redacted]

E. Biopharmaceutics Considerations

BCS Classification is not applicable since the drug product is an injectable solution. Based on review of biopharmaceutical aspects of NDA submission, the differences in inactive ingredients between the RLD and the proposed formulation are not expected to affect the bioavailability of sodium nitroprusside in the proposed drug product when administered via the intravenous infusion. In addition, the difference in the administered volume and infusion rate are not expected to affect the safety and efficacy of the proposed drug product. The applicant's request for a waiver of the requirement to conduct in vivo BA/BE studies for the proposed drug product is granted.

F. Any Special Product Quality Labeling Recommendations

Per NDA submission, the applicant proposed to label the product as: Sodium Nitroprusside (b) (4) Injection. However, the applicant was alerted to the fact that usage of term " (b) (4) injection" is not acceptable. To comply with *USP General Chapter <1121> Nomenclature*, we recommended labeling the product as follows: Sodium Nitroprusside in 0.9% Sodium Chloride Injection or Proprietary name (Sodium Nitroprusside) in 0.9% Sodium Chloride Injection. The applicant accepted the Agency recommendations. Sodium nitroprusside solution is (b) (4) [redacted] Sodium nitroprusside should be clear colorless to red/brown in color; and is not to be used if solution is blue, green, or bright red

G. Manufacturing Facilities Pertaining Recommendations

The Office of Process and Facilities has issued an overall acceptable recommendation for all the relevant manufacturing and testing facilities.

H. Life Cycle Knowledge Management

Final Risk Assessment

NDA 209387 (Sodium Nitroprusside in 0.9% Sodium Chloride Injection)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors Affecting CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Sterility	Formulation Container Closure Process Parameters Scale/equipment/ site	**H** **(High; RPN 100)**	Microbial testing i.e., sterility (USP <71>), bacterial endotoxins (USP <85>) and container/closure integrity testing (USP <1207>) are performed on product release. Process validation information relevant to microbiological testing is adequate.	Acceptable	Given that the product sterility is the high risk attribute, any proposed changes in (b) (4) manufacturing process or microbiological testing-related product specification may need to be carefully evaluated.
Endotoxin Pyrogen	Formulation Container Closure Process Parameters Scale/equipment/ site	**M** **(Moderate; RPN 32)**	Endotoxin testing is performed on product release per USP<85>, and acceptance limits have been set in compliance with USP requirements based on the maximum total daily dose.	Acceptable	Any proposed changes in acceptance criteria for endotoxin levels will need to be carefully evaluated in the context of acceptable limits based on the maximum total daily dose.
Assay (active), stability	Formulation Container Closure Process Parameters Scale/equipment/ site	L (Low; RPN 6)	Stability of API has been demonstrated. Two identification tests are included in product specification. Manufacturing process is reasonably well-controlled.	Acceptable	
Uniformity of Dose – Fill/ deliverable Volume	Formulation Container Closure Process Parameters Scale/equipment/ site	L (Low; RPN 8)	The strategy for overfill is aligned with the USP <1151> and ensures minimal extractable volume of 100 mL.	Acceptable	
Osmolality	Formulation Container Closure Process Parameters Scale/equipment/ site	L (Low; RPN 12)	Osmolality is monitored on release with acceptance limits (270-310 mOsm/kg) within the physiological range.	Acceptable	

Final Risk Assessment (continued)

NDA 209387 (Sodium Nitroprusside in 0.9% Sodium Chloride Injection)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors Affecting CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
pH (High)	Formulation Container Closure Process Parameters Scale/equipment/ site	L (Low; RPN 12)	Product pH (USP <791> with acceptance limits of (b) (4)	Acceptable	
Particulate Matter	Formulation Container Closure Process Parameters Scale/equipment/ site	**M** **(Moderate; RPN 45)**	Particulate matter (b) (4) (b) (4) µm) is monitored on product release.	Acceptable	
Leachable Extracts	Formulation Container Closure Process Parameters Scale/equipment/ site	L (Low; RPN 24)	All results from extractable testing per USP (b) (4) using (b) (4) as solvent are acceptable.	Acceptable	
Appearance	Formulation Container Closure Process Parameters Scale/equipment/ site	L (Low; RPN 9)	Sodium nitroprusside solution is (b) (4) . Product and container closure appearance is (b) (4) Product stability is well demonstrated using commercial container closure system.	Acceptable	

EXECUTIVE SUMMARY: OVERALL ASSESSMENT AND FINAL RECOMMENDATION

Application Technical Lead (ATL) Assessment and Signature:

From the chemistry, manufacturing, and controls (CMC) perspective, NDA 209387 (Sodium Nitroprusside in 0.9% Sodium Chloride Injection) is recommended for approval.

Mohan Sapru, M.S., Ph.D.
ATL
ONDP/DNDPI/NDPBI

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ENVIRONMENTAL ANALYSIS

R Regional Information

Environmental Analysis

Pursuant to 21 CFR §25.31 (a), Exela Pharma Sciences LLC (Applicant) claimed a categorical exclusion from the requirements of an Environmental Impact Analysis. Also stated that action on the NDA does not increase the use of the active moiety. The applicant also certified that to the best of their knowledge and opinion, the manufacturing facilities located at Lenoir, NC are in compliance with all federal, state, and local environmental protection requirements and that it has a certified waste disposal program.

Reviewer's Assessment: Acceptable. Sodium Nitroprusside Injection is being used in clinic since several years and the FDA had approved an NDA for Nitropress® (sodium nitroprusside) Injection previously. Therefore, approval of the current NDA will not increase the use of the active ingredient. The only difference between the current formulation and the approved formulation is the concentration and excipient. The current formulation contains sodium chloride whereas Nitropress contains no excipient other the Water for Injection. Raanan Bloom of the EA team in OPQ was also contacted and he indicated that the above categorical exclusion statement is acceptable for granting the categorical exclusion because the sodium nitroprusside is an approved drug and is used currently.

Primary EA Reviewer Name and Date: Rao V. Kambhampati, Ph.D. 1/24/17

Secondary Reviewer Name and Date: Wendy Wilson-Lee, Ph.D. 1/24/17

LABELING

R Regional Information

1.14 Labeling

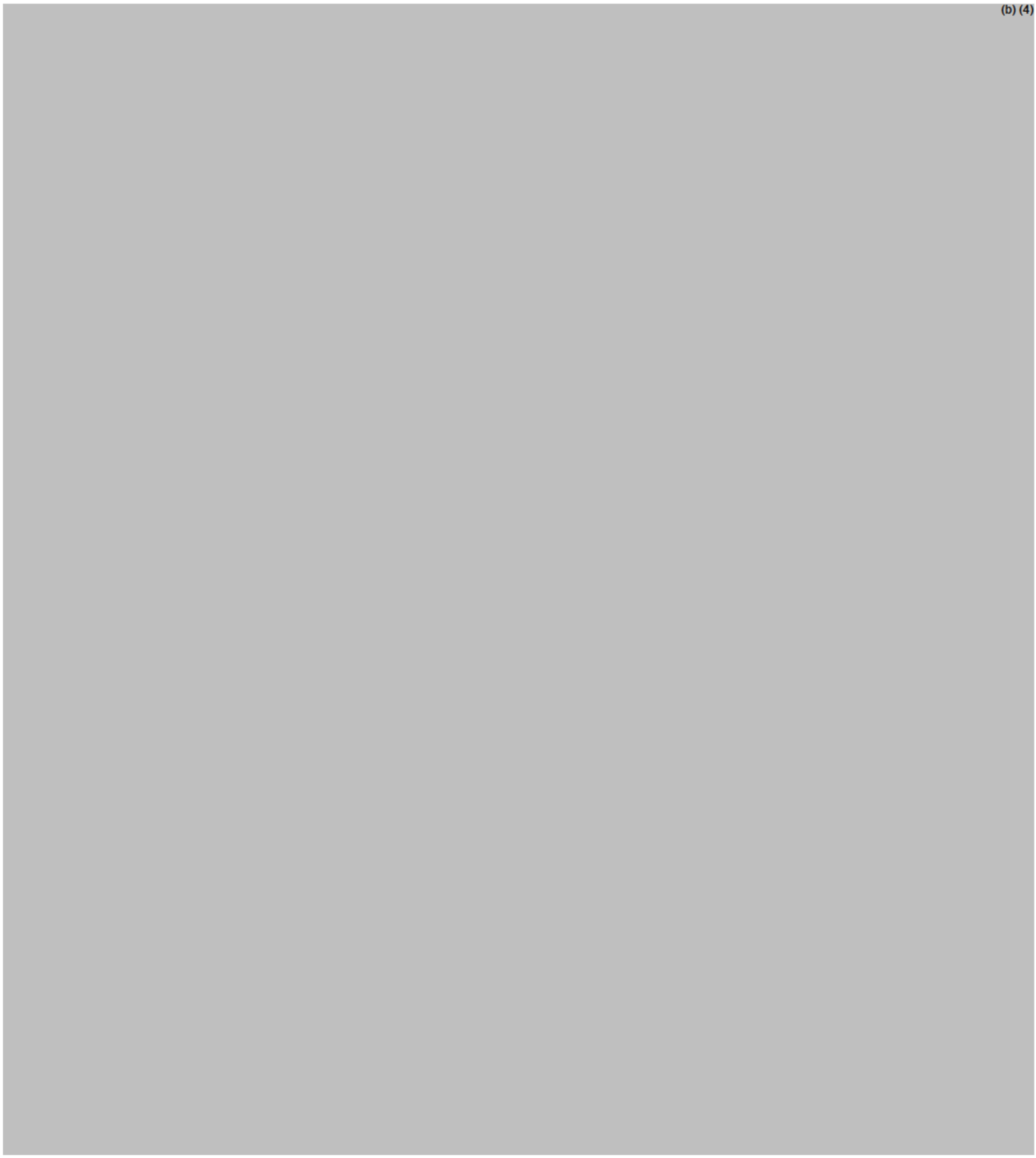
Immediate Container Label

(b) (4)

Reviewer's Assessment: Acceptable. The above revised vial label complies with all the regulatory requirements from the CMC perspective.

Carton Labeling

(b) (4)



List of Deficiencies: None

Primary Labeling Reviewer Name and Date: Rao V. Kambhampati, Ph.D. 1/24/2017

Secondary Reviewer Name and Date: Wendy Wilson-Lee, Ph.D. 1/24/2017

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CHAPTER VII: Biopharmaceutics

NDA: 209387

Drug Product Name: Sodium Nitroprusside in 0.9% Sodium Chloride Injection

Strength(s): 50 mg/100 mL (0.5 mg/mL)[1]

Route of Administration: Intravenous (IV)

Applicant Name: Exela Pharma Sciences

EXECUTIVE SUMMARY:

NDA 209387 is submitted as a 505(b)(2) application. The proposed drug product, Sodium Nitroprusside in 0.9% Sodium Chloride Injection, is a parenteral solution for administration by injection, and the proposed drug product has the same active ingredient (sodium nitroprusside), and has the same dosage form, route of administration [IV infusion] and indication as the listed drug (LD), Nitropress® (sodium nitroprusside injection). However, the proposed product and the LD product on dilution are different with regard to the inactive ingredients [sodium chloride vs. dextrose] and the concentration of the active ingredient. As supported by the additional information [pH, osmolality and literature], the differences in inactive ingredients are not expected to affect the bioavailability of sodium nitroprusside in the proposed drug product when administered via the intravenous (IV) infusion route. In addition, the difference in the administered volume and infusion rate are not expected to affect the safety and efficacy of the proposed drug product. The Applicant's request for a waiver of the requirement to conduct in vivo BA/BE studies for the proposed drug product, Sodium Nitroprusside in 0.9% Sodium Chloride Injection 50 mg/100 mL (0.5 mg/mL), is granted.

From the Biopharmaceutics perspective, NDA 209387 for Sodium Nitroprusside in 0.9% Sodium Chloride Injection 50 mg/100 mL (0.5 mg/mL), is recommended for **APPROVAL.**

[1] 100 mL single-dose glass vial

SUBMISSION:

Exela submitted the current NDA for Sodium Nitroprusside in 0.9% Sodium Chloride Injection, 50 mg/100 mL (0.5 mg/mL), for IV infusion use under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. This 505 (b)(2) application relies for approval, on FDA's findings of safety and effectiveness for the listed drug (LD), Nitropress® (sodium nitroprusside injection), marketed by Hospira under the approved ANDA 071961.

BIOPHARMACEUTICS REVIEW:

The LD, Nitropress® (sodium nitroprusside injection), is available as a 2 mL vial, 25 mg/mL (50 mg/2 mL). The LD is not suitable for direct injection. The solution must be further diluted in sterile 5% dextrose injection to yield a final diluted concentration of 50 mcg/mL-200 mcg/mL, before infusion. The LD label[2] also provides a table for the infusion rates corresponding to the recommended initial and maximal doses (0.3 mcg/kg/min and 10 mcg/kg/min, respectively) for both adult and pediatric patients of various weights.

Indications and usage: Sodium Nitroprusside for Injection is a vasodilator drug indicated in use of adult and pediatric patients for:

Immediate reduction of blood pressure
Producing controlled hypotension to reduce bleeding during surgery
Treatment of acute (b) (4) heart failure

Exela's proposed drug product, Sodium Nitroprusside in 0.9% Sodium Chloride Injection, is intended for intravenous infusion and is suitable for direct injection/infusion without further dilution. The proposed drug product is provided as a 100 mL vial [0.5 mg/mL, 50 mg/100 mL, (b) (4)]. The concentration of Exela's proposed drug product, (b) (4) is greater than the highest concentration of the LD diluted per the labeling, 200 mcg/mL; therefore, the proposed labeling of Exela's drug product contains a modified dosing table. The infusion rates corresponding to the recommended initial and maximal doses of sodium nitroprusside (0.3 mcg/kg/min and 10 mcg/kg/min) are the same for the LD and the proposed drug product.

Biowaiver Request:

The NDA submission includes a biowaiver request for Sodium Nitroprusside in 0.9% Sodium Chloride Injection intended solely for intravenous administration citing 21 C.F.R. 320.22(b) (1). ANDA 071961, Nitropress® (sodium nitroprusside injection), was identified as the listed drug (LD) product as the basis for the submission.
Exela's Sodium Nitroprusside in 0.9% Sodium Chloride Injection differs from the listed drug with respect to the active ingredient concentration and inactive ingredients present in the LD. The LD product contains only Water for Injection other than the drug

[2] Appendix provides the table for the infusion rates needed for the proposed product and the LD product.

substance whereas Exela's formulation contains 9 mg/mL Sodium Chloride, USP (b) (4) agent).

Table 1 below, provides the quantitative and qualitative compositions of the listed drug, Nitropress® Concentrate, Nitropress® diluted infusion solution, and Exela's proposed drug product, Sodium Nitroprusside in 0.9% Sodium Chloride Injection.

Table 1: Formulation comparison between the LD Nitropress® (Sodium Nitroprusside Injection) Concentrate, Nitropress® (Sodium Nitroprusside Injection) Diluted Infusion Solution, and Exela's Sodium Nitroprusside (b) (4) Injection[3]

	Listed Drug Product (NITROPRESS®) (Sodium Nitroprusside Injection) Concentrate	Listed Drug Product (NITROPRESS®) (Sodium Nitroprusside Injection) Diluted Infusion Solution - 250 - 1000 mL in sterile 5% Dextrose Injection*	Exela's Proposed Drug Product, Sodium Nitroprusside (b) (4) Injection
Total Dose of Sodium Nitroprusside per container	50 mg	50 mg	50 mg
Sodium Nitroprusside Concentration	25 mg/mL	0.2 mg/mL – 0.05 mg/mL	0.5 mg/mL
Sodium Chloride	None	None	9 mg/mL (0.9%)
Dextrose	None	(b) (4) (5%)	None
Water	(b) (4)		
Dosage Form	Injection, Solution, Concentrate	Injection, Solution	Injection, Solution
Administered Dose	None	0.3 to 10 mcg/kg/min	0.3 to 10 mcg/kg/min
Administered Volume	None	(b) (4)	

* per the NITROPRESS® labeling, revision 02/15

** When administering the 0.2 mg/mL (NITROPRESS®) (Sodium Nitroprusside Injection) Diluted Infusion Solution

A comparative summary of the measured physiochemical data for the diluted listed drug product, Nitropress® diluted infusion solution and Exela's proposed drug product, Sodium Nitroprusside in 0.9% Sodium Chloride Injection, is provided in Table 2 below. The measurements of the physiochemical properties were performed in triplicate for one lot of diluted LD product and three (3) lots of Exela's proposed drug product.

[3] Sodium Nitroprusside in 0.9% Sodium Chloride Injection

Table 2: Comparison of physicochemical data of the LD, Nitropress® diluted infusion solution and Exela's proposed drug product, Sodium Nitroprusside in 0.9% Sodium Chloride Injection[4]

Physiochemical Parameter	NITROPRESS® Diluted Infusion Solution *	Exela's Sodium Nitroprusside (b) (4) Injection		
Density		(b) (4)		
pH				
Osmolality	265 mOsm/kg 262 mOsm/kg 263 mOsm/kg	XLNF1545 289 mOsm/kg 289 mOsm/kg 291 mOsm/kg	XLNF1546 290 mOsm/kg 290 mOsm/kg 290 mOsm/kg	XLNF1547 289mOsm/kg 289 mOsm/kg 291 mOsm/kg

* When diluted in 250 mL of 5% Dextrose Injection as per the NITROPRESS® labeling, revision 02/15

Justification of the differences observed in the physicochemical data

Osmolality: The osmolality of Exela's proposed drug product is slightly higher, about 27 units, than the diluted listed drug product. The difference in the measured osmolality is primarily due to the difference in the diluent of the two drug products, specifically, 5% Dextrose Injection and 0.9% Sodium Chloride for the LD and Exela's proposed drug product respectively. The typical measured osmolality of 5% Dextrose Injection is about 253 mOsm/kg compared to the typical measured osmolality of 0.9% Sodium Chloride Injection, about 290 mOsm/kg. The measured osmolality of both drug products 263 mOsm/kg and 290 mOsm/kg are close in relation to the osmolality of the extracellular fluid, about 280 mOsmol/kg, thus are both considered isotonic.

pH: The pH of Exela's proposed drug produc (b) (4) than the diluted LD product. The difference in the measured pH is primarily due to the difference in the diluent of the two drug products, specifically, 5% Dextrose Injection and 0.9% Sodium Chloride for the listed drug and Exela's proposed drug product respectively.

[4] In the initial submission, Sodium Nitroprusside in 0.9% Sodium Chloride Injection was called Sodium Nitroprusside (b) (4) Injection

Administered volume and rate:

The administered volume and rate with Exela's proposed product is less compared to that of the diluted LD product. Exela's proposed drug product is proposed to be infused at a lower rate so that sodium nitroprusside is dosed (as mcg/kg/hr) at the same rate as that for the diluted listed drug product (Table 3).

The difference in both the administered volume and rate is due to the difference in concentration of Sodium Nitroprusside in Exela's proposed drug product, 0.5 mg/mL and the diluted listed drug product, 0.05 mg/mL to 0.2 mg/mL. Regardless of the administration volume or rate, both the diluted listed drug product and Exela's proposed drug product provide a total dose of 50 mg Sodium Nitroprusside.

Table 3: Comparative data for administration conditions for the LD and the proposed product

	Nitropress® - IV (diluted)	Exela's Proposed Drug Product
Administration rate (volume of fluid)	(b) (4)	
Administration rate (mcg of Sodium Nitroprusside)	0.3 mcg/kg/min – 10 mcg/kg/min	0.3 mcg/kg/min – 10 mcg/kg/min

Reviewer's Assessment:

The proposed drug product is proposed to be infused at a lower rate so that the active, sodium nitroprusside, is dosed (as mcg/kg/hr) at the same rate as that for the diluted LD product.
Sodium nitroprusside has a short half-life and rapid disposition kinetics; the differences in the administered volume of fluid in 1 hour (b) (4) are not likely to affect the disposition kinetics of sodium nitroprusside therefore these differences are acceptable.

Sodium chloride: Sodium chloride is present in Exela's proposed drug product at 0.9 mg/mL or 0.9 g/100 mL (b) (4) whereas the LD product concentrate and the diluted listed drug product contain no sodium chloride. The listed drug product concentrate contains no added (b) (4) agent as the concentrate must be diluted in 250 – 1000 mL of 5% Dextrose Injection prior to administration.

Dextrose: Dextrose is not present in Exela's proposed drug product; however, it is present in the diluted LD product as a result of the dilution of the concentrate in 5% Dextrose Injection. The diluted listed drug product contains about 12.5 grams of Dextrose when diluted with 250 mL of 5% Dextrose Injection and up to 50 grams of Dextrose when diluted with 1000 mL of 5% Dextrose Injection. Both dextrose and sodium chloride

are known to function as [redacted] (b) (4), and both the Exela's proposed drug product and the diluted listed drug product solutions are considered [redacted] (b) (4).

The dose of sodium nitroprusside administered is the same either with the LD or Exela's proposed drug product and needs to be titrated from an infusion rate of about 0.3 mcg/kg/min to an average infusion rate of about 3 mcg/kg/min (a maximum rate of 10 mcg/kg/min).The diluted LD product (0.2 mg/mL, 0.1 mg/mL, or 0.05 mg/mL) and Exela's proposed drug product (0.5 mg/mL) vary in the concentration of the dosing solutions, which results in differences in the volume of solution infused even though the total dose of sodium nitroprusside delivered is the same.

The Applicant stated that several clinical studies reported in the literature have used sodium nitroprusside infusion solutions prepared with normal saline and not with D5W as recommended in the LD labeling. Some of the reported studies that use normal saline as diluent are summarized in the Table 4 below. It is noted that none of the products in the literature was a ready-to-use long term storage stable product like that of Exela's proposed product. However, the literature shows a wide range of concentrations and infusion rates that are efficacious with no adverse effects attributed to dilution with normal saline.

Table 4: Clinical studies using sodium nitroprusside diluted in normal saline

Reference	N	
Schlant, RC, 1962[5]	30	Thirteen normotensive subjects and seventeen subjects with clinically diagnosed diastolic hypertension received sodium nitroprusside (0.06 mg/mL) in normal saline. Infusion rates ranged from 0.61 to 7.66 mcg/kg/min. The results obtained indicate that intravenously administered sodium nitroprusside does cause a reduction in the calculated total peripheral resistance in normotensive and hypertensive human beings.
Miller, RR, 1975[6]	12	Twelve patients with chronic coronary pump dysfunction received sodium nitroprusside infusion during diagnostic cardiac catheterization to lower systolic pressure to 95-105 mm Hg. Sodium nitroprusside solution in normal saline at a concentration of 50 mcg/mL was administered at rates ranging from 25 to 100 mcg/min with an average rate of 63 mcg/min. Nitroprusside was shown to improve left ventricular function.
Robinson, BF, 1979[7]	4	The effect of sodium nitroprusside on the dilation in forearm arterial bed and preconstricted dorsal hand vein were evaluated. Sodium nitroprusside was infused in normal saline at rates of 0.67 to 2.68 nmol/min (175 to 702 ng/min), to study forearm blood flow. Continuous infusion of sodium nitroprusside in normal saline at rates of 16.8 to 67.1 pmol/min (4.4 ng to 17.6 ng/min) was also administered. Sodium nitroprusside was shown to be ten times more effective in veins than arterioles.

[5] Schlant, RC, et.al., Studies on the acute cardiovascular effects of intravenous sodium nitroprusside, The American Journal of Cardiology, 9: 51-59, 1962

[6] Miller, RR, et.al., Clinical use of sodium nitroprusside in chronic ischemic heart disease, Circulation, 51: 328-336, 1975

[7] Robinson, BF, et.al., Comparative dilator effect of verapamil and sodium nitroprusside in forearm arterial

Tarhan, F, 2004[8]	21	Patients with idiopathic detrusor overactivity underwent cystometries and 50 mL of sodium nitroprusside (7.2 mM; 1.89 mg/mL) was administered into the bladder which was drained after 30 min. The results showed that intravesical administration of sodium nitroprusside is not an effective treatment for detrusor overactivity.
Amit, G, 2006[9]	48	Patients presenting with ST-elevation myocardial infarction (STEMI) were dosed with 60 mcg of sodium nitroprusside in 5 mL (12 mcg/mL) normal saline as an intracoronary bolus injection. In patients with STEMI, fixed dose sodium nitroprusside failed to improve coronary flow and myocardial tissue perfusion but improved clinical outcomes at 6 months.

The Applicant reported that in humans, the volume of extracellular fluids is typically 15 L, of which 12 L is interstitial fluid and 3 L is plasma. Interstitial fluid makes up 16% of human body weight, and blood plasma, 4%. Because of the rapidity with which sodium nitroprusside is distributed, there is little opportunity for the differences in infusion solution volume (250 mL for the LD vs 100 mL for Exela's proposed drug product for a total dose of 50 mg sodium nitroprusside) or excipients to play a meaningful role either in the extracellular distribution or in the reaction with Hgb. Again, there have been no literature reports indicating that either D5W, or normal saline would have any influence on the distribution or clearance of sodium nitroprusside.

The Applicant further stated that, in addition to the unique ultra-short half-life and rapid disposition kinetics, the LD labeling also establishes that the disposition of sodium nitroprusside is not affected by the dose. For example, the LD labeling identifies several dosing scenarios that range from 0.3 mcg/kg/min to 10 mcg/kg/min, a 30-fold dosing range. The labeling further indicates that at any of these doses, the onset and offset of hypotensive action by sodium nitroprusside is very rapid, literally coinciding with, or staying below, the circulatory half-life of about 2 minutes or less. Therefore, the variations within this range of dosing should not have an impact on sodium nitroprusside disposition in humans. The Applicant claimed that the pharmacodynamics effect and the disposition kinetics appear to be robust, and are not dose-sensitive in the recommended dosing range. Therefore, the effects of excipients, if any, that could potentially lead to dosing variations and/or availability of the drug, would not be significant.

Reviewer's Assessment:

The osmolality of the Applicant's proposed drug product is slightly higher than the osmolality of the diluted LD. The osmolality of the Applicant's proposed drug product is approximately 290 mOsm/kg, which is similar to the osmolality of 0.9% Sodium Chloride. The osmolality difference between the Applicant's proposed drug product and the diluted LD are minor and acceptable. The pH of the Applicant's proposed drug

bed and dorsal hand veins in man: functional differences between vascular smooth muscle in arterioles and veins, Cardiovascular Research, 13: 16-21, 1979

[8] Tarhan, F, et.al., The effect of intravesicle sodium nitroprusside on idiopathic detrusor overactivity, Urol Res, 32: 200-203, 2004

[9] Amit, G, et.al., Intracoronary nitroprusside for the prevention of the no-reflow phenomenon after primary percutaneous coronary intervention in acute myocardial infarction: a randomized, double blind, placebo-controlled clinical trial, American Heart Journal, 152: 887.e10-887e14, 2006

product is approximately (b) (4), which is slightly (b) (4) than the pH of the diluted LD (pH (b) (4)). The pH difference between the Applicant's proposed drug product and the diluted LD are minor and are not expected to affect the efficacy and or safety of the drug product.

The Applicant's proposed drug product is formulated in 0.9% Sodium Chloride whereas the LD is to be diluted in 5% Dextrose Injection prior to infusion. Both dextrose and sodium chloride are known to act as (b) (4) vehicles. The major differences in the Applicant's proposed drug product and diluted LD are the amounts of sodium chloride and dextrose. The human pharmacokinetics and pharmacodynamics show that the disposition of the sodium nitroprusside is rapid and are not influenced by variations in dosing rates over a wide range. The Applicant reported that several clinical studies reported in the literature have used sodium nitroprusside infusion solutions prepared with normal saline and not with dextrose as recommended in the LD labeling.

This Reviewer agrees that the slight differences in the pH and osmolality and the differences in the amounts of sodium chloride and dextrose are not likely to affect the disposition of sodium nitroprusside; therefore these differences are acceptable.

Sodium chloride load: The sodium chloride present in the proposed drug product is to render the solution (b) (4) as the drug product is ready to use and requires no dilution prior to administration. At the maximum rate of infusion ((b) (4) **hour**) of the proposed drug product (b) (4) mg of NaCl will be administered in 1 hour i.e. approximately (b) (4) mg of Na/hour from (b) (4) mg of NaCl. Additional (b) (4) mg of Na will be administered from Sodium Nitroprusside Injection in 1 hour [same for the LD and the proposed product].i.e. approximately (b) (4) **mg** of Na/hour will be administered using the proposed drug product.

During the Mid-Cycle meeting (Monday, October 03, 2016), the issue of sodium chloride load was discussed with the Clinical team. The Clinical team was asked if the amount of sodium is acceptable or is there any safety concern since the patients are hypertensive. The Clinical team stated that there appears to be no concerns regarding the sodium amounts, however, this issues will be addressed in the Clinical Review.

Reviewer's Final Assessment: Adequate

This 505 (b)(2) Application relies, for its approval, on FDA's findings of safety and effectiveness for the LD. In addition, this Application is supported with data obtained from the scientific literature. This NDA includes a request to waive the requirement to conduct bioavailability/bioequivalence study(ies). According to 21 CFR 320.22(b)(1), a drug product's in vivo bioavailability or bioequivalence may be considered self-evident and a waiver of in vivo studies may be granted if the drug product meets the following criteria:

"It is a parenteral solution intended solely for administration by injection, and contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application."

The proposed drug product is a parenteral solution for administration by injection, and the proposed drug product has the same active ingredient (sodium nitroprusside), and has the same dosage form, route of administration and indication as the LD.

However, the proposed product and the reference product are different with regard to the inactive ingredients [sodium chloride vs. dextrose] and the concentration of the active ingredient. As supported by the additional information [pH, osmolality and literature], the differences in inactive ingredients are not expected to affect the bioavailability of sodium nitroprusside in the proposed drug product when administered via IV infusion route.

Although, the criteria for a biowaiver under 21 CFR 320.22(b)(1) is not fully met, based on 21 CFR 320.24(b)(6), the FDA can rely on any other approach deemed adequate to establish the bridge (bioavailability/bioequivalence) between the listed and proposed drug products.

Specifically for NDA 209387, the differences in inactive ingredients not expected to have an impact on the disposition of sodium nitroprusside from the Applicant's proposed formulation as compared to the reference formulation. In addition, the difference in the administered volume and infusion rate are not expected to affect the safety and efficacy of the proposed drug product. Therefore, the Applicant's request for a waiver of the requirement to conduct in vivo BA/BE studies for their proposed product, Sodium Nitroprusside in 0.9% Sodium Chloride Injection 50 mg/100 mL (0.5 mg/mL), is granted.

RECOMMENDATION

A waiver of the in vivo bioequivalence study requirement is granted.

From the Biopharmaceutics perspective, NDA 209387 for Sodium Nitroprusside in 0.9% Sodium Chloride Injection 50 mg/100 mL (0.5 mg/mL), is recommended for **APPROVAL**.

Om Anand, Ph.D. [Date: 1/25/2017]

Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drug Products/OPQ

I concur with Dr. Om Anand's assessment and recommendation.

Elsbeth Chikhale, Ph.D. [Date: 1/25/2017]

Acting Biopharmaceutics Lead
Division of Biopharmaceutics
Office of New Drug Products/OPQ

Appendix 1:

Table 5: Infusion rates (mL/hour) to achieve Initial (0.3 mcg/kg/min), average (3 µg/kg/min) and maximal (10 mcg/kg/min) dosing of Sodium Nitroprusside in 0.9% Sodium Chloride Injection

Volume		100 mL		
Sodium Nitroprusside in 0.9% Sodium Chloride Injection		50 mg		
Concentration			(b) (4)	
Weight		Initial Rate 0.3 µg/kg/min	Average Rate 3 µg/kg/min	Maximal Rate 10 µg/kg/min
kg	lbs	Infusion Rate (mL/hour)		
10	22	0.36	3.6	12.0
15	33	0.54	5.4	18.0
20	44	0.72	7.2	24.0
25	55	0.90	9.0	30.0
30	66	1.08	10.8	36.0
35	77	1.26	12.6	42.0
40	88	1.44	14.4	48.0
45	99	1.62	16.2	54.0
50	110	1.80	18	60.0
55	121	1.98	19.8	66.0
60	132	2.16	21.6	72.0
65	143	2.34	23.4	78.0
70	154	2.52	25.2	84.0
75	165	2.70	27.0	90.0
80	176	2.88	28.8	96.0
85	187	3.06	30.6	102.0
90	198	3.24	32.4	108.0
95	209	3.42	34.2	114.0
100	220	3.6	36.0	120.0

Table 6: Infusion rates (mL/hour) to achieve initial (0.3 mcg/kg/min), average (3 µg/kg/min) and maximal (10 mcg/kg/min) dosing of the LD Nitropress

Volume NITROPRESS concentration		250 mL 50 mg 200 mcg/mL		500 mL 50 mg 100 mcg/mL		1000 mL 50 mg 50 mcg/mL	
pt weight							
kg	**lbs**	**init**	**max**	**init**	**max**	**init**	**max**
10	22	1	30	2	60	4	120
20	44	2	60	4	120	7	240
30	66	3	90	5	180	11	360
40	88	4	120	7	240	14	480
50	110	5	150	9	300	18	600
60	132	5	180	11	360	22	720
70	154	6	210	13	420	25	840
80	176	7	240	14	480	29	960
90	198	8	270	16	540	32	1080
100	220	9	300	18	600	36	1200

Elsbeth Chikhale

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Om Anand

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MICROBIOLOGY

Product Background:

NDA: 209387

Drug Product Name / Strength: Sodium Nitroprusside (b) (4) Injection, 50 mg/100 mL

Route of Administration: IV

Applicant Name: Exela Pharma Sciences, LLC.

Manufacturing Site:
Exela Pharma Sciences
(b) (4)
Lenoir, NC 28645.
Telephone Number: (828) 758-5474
Fax Number: (828) 757-7888

Method of Sterilization: (b) (4)

Review Summary:

List Submissions being reviewed (table):

Submit	Received	Assigned to Reviewer
5/6/2016	5/9/2016	5/23/2016
8/11/2016*	8/11/2016	N/A
9/22/2016*	9/23/2016	N/A

*response to information request

Highlight Key Outstanding Issues from Last Cycle: N/A
Concise Description Outstanding Issues Remaining: N/A
The submission is recommended for approval on the basis of sterility assurance.

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q)
MODULE 3.2: BODY OF DATA

P.1 Description of the Composition of the Drug Product

- **Description of drug product –** Sterile, unpreserved, clear, light tan solution

- **Drug product composition –**

Ingredient	Content per mL	Function
Sodium Nitroprusside	0.5 mg	API
Sodium Chloride	9 mg	(b) (4)
(b) (4)	N/A	
WFI	q.s.	

- **Description of container closure system –**

Configuration	Component	Description	Manufacturer
50 mg/100 mL	Vial	100 mL, USP Type I Amber Glass (b) (4)	(b) (4)
	Stopper	(b) (4)	(b) (4)
	Seal		

Reviewer's Assessment: Acceptable

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- **Container-Closure and Package integrity -** (M3/32p2/microbiological-attributes.pdf)

(b) (4)

(b) (4)

Reviewer's Assessment: Acceptable

- **Antimicrobial Effectiveness Testing -**

  N/A. The subject drug product is a single dose; antimicrobial effectiveness testing is not required.

Reviewer's Assessment: Acceptable

P.3 Manufacture

P.3.1 Manufacturers

Exela Pharma Sciences, LLC
(b) (4)
Lenoir, NC 28645

(b) (4)

Exela Pharma Sciences is responsible for manufacturing of the drug product. Exela and (b) (4) will perform the release and stability testing of the drug product.

P.3.3 Description of the Manufacturing Process and Process Controls

(b) (4)

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Reviewer's Assessment: Acceptable

R REGIONAL INFORMATION

R.1 Executed Batch Record

Executed lot #(s): XLNF1545, XLNF1546, XLNF1547, XLNC1604

The batch records confirm that validated sterilization (b) (4) were used for the manufacture of the exhibit batch.

Reviewer's Assessment: Acceptable

2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

A. PACKAGE INSERT

(1.14)

Storage temperature: Store at 20 to 25°C; Route of administration: IV

(b) (4)

Information Request:

The following comments were conveyed to the sponsor in an IR letter dated 9/19/2016. The response was received on 9/23/2016. The original comments followed by the response are included below in italics.

(b) (4)

(b) (4)

Response: *The drug product is ready to use and does not require dilution prior to use; therefore, the additional study (risk assessment) is not required. The package insert was revised to indicate direct injection.*

Reviewer's Assessment: Acceptable

Microbiology Deficiencies: None

Primary Microbiology Reviewer Name and Date:

Yuansha Chen, Ph.D. 12/16/2016

CDER/OPF/DMA

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

Neal, J. Sweeney, Ph.D. 12/20/2016

CDER/OPF/DMA

Neal Sweeney

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Yuansha Chen

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