CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208083Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: Approval

NDA 208083
Review # 1

Drug Name/Dosage Form	Clindamycin in 0.9% Sodium Chloride Injection
Strength	300 mg/50 mL, 600 mg/50 mL, and 900 mg/50 mL
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Celerity Pharmaceuticals, LLC
US agent, if applicable	John Oberholtzer

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA	June 30, 2016	All
Quality Amendment	November 4, 2016	Process
Quality Amendment	November 14, 2016	Microbiology
Quality Amendment	December 12, 2016	Facilities
Quality Amendment	February 15, 2016	Drug Product
Quality Amendment	March 31, 2016	Drug Product
Quality Amendment	April 5, 2016	Drug Product

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Haripada Sarker	Branch I/DNDAPI
Drug Product	Suresh Pagay Yushi Feng	Branch III/DNDP I
Process	Masihuddin Jaigirdar	Branch VII/DPA
Microbiology	Lisa Shelton	Branch II/DMA
Facility	Wenzheng (Wendy) Zhang	Branch II/DIA
Biopharmaceutics	Kaushalkumar Dave	Branch I/ DBP
Environmental Analysis (EA)	Suresh Pagay	Branch III/DNDP I
Regulatory Business Process Manager	Luz Rivera	Branch I/DRBPM I
Application Technical Lead	Dorota Matecka	Branch III/DNDP I

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)	Clindamycin Phosphate	Adequate	May 24, 2016 April 13, 2017	Review by Humcha K Hariprakasha Review by Haripada Sarker
	Type III	Baxter	Galaxy Plastic Containers	Adequate	October 9, 2015 September 26, 2016	Review by Wendy Tan Microbiology reviews D6344M03R01.doc and D6344M03R02.doc by Yarery Smith

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
preNDA Meeting	NDA 208083	Meeting minutes in DARRTS
NDA (Listed Drug)	NDA 50639	

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	Complete	Adequate	4/14/17	Tessie Alapatt
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

NDA 208083 is recommended for approval by the Office of Pharmaceutical Quality. The NDA, as amended, has provided sufficient chemistry, manufacturing and controls information to assure the identity, strength, purity, and quality of the drug product, clindamycin in 0.9% sodium chloride injection. All information requests and review issues have been addressed and there are no pending approvability issues. The manufacturing and testing facilities for this NDA are deemed acceptable and an overall "Approve" recommendation was entered into Panorama by the Office of Process and Facilities (OPF) on April 14, 2017.

II. Summary of Quality Assessments

A. Product Overview

Clindamycin is a lincosamide antibacterial indicated for the treatment of the following:

- Serious infections caused by susceptible anaerobic bacteria
- Infections Due to Susceptible Strains of Streptococci, Pneumococci and Staphylococci
- Lower Respiratory Tract Infections
- Skin and Skin Structure Infections
- Gynecological Infections
- Intra-abdominal Infections
- Septicemia
- Bone and Joint Infections

This 505(b)(2) NDA provides for a new injectable formulation of clindamycin to be used for the treatment of the same infections as listed in the listed drug labeling. The listed drug for this 505(b)(2) NDA is CLEOCIN PHOSPHATE IV Solution (clindamycin injection in 5% dextrose) in the GALAXY plastic containers (300 mg/50 mL, 600 mg/50 mL, and 900 mg/50 mL) approved under NDA 50639 and held by Pfizer. The currently proposed drug product is a new formulation of clindamycin injection, and includes a different tonicity adjuster as compared with the listed drug; i.e., 0.9% w/v sodium chloride versus 5% w/v dextrose used in the formulation of the listed drug. The currently proposed drug product is also supplied in the GALAXY plastic containers.

Proposed Indication(s) including Intended Patient Population	As listed above (adults and pediatric patients)
Duration of Treatment	The recommended dosing regimen for Clindamycin in 0.9% Sodium Chloride Injection is 600-1200 mg/day in 2, 3, or 4 equal doses by intravenous infusion for

	serious infections; For more severe infections, the recommended dosing regimen is 1200-2700 mg/day in 2, 3, or 4 equal doses by intravenous infusion
Maximum Daily Dose	As above (see the package insert for details)
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Clindamycin phosphate drug substance [redacted] (b) (4)

The chemistry manufacturing and controls information for clindamycin phosphate drug substance has been provided via a reference to DMF Type II [redacted] (b) (4). DMF [redacted] (b) (4) has been found to be adequate via a chemistry review dated May 24, 2016 conducted for another referenced application. In addition, the two minor amendments recently submitted to the DMF were also reviewed in support of the current NDA and found to be acceptable (review dated April 13, 2017, in DARRTS). The retest period established by the drug substance manufacturer for clindamycin phosphate stored [redacted] (b) (4) months. However, the retest period established by the current drug product manufacturer for clindamycin phosphate drug substance is [redacted] (b) (4) months.

The drug product, clindamycin in 0.9% sodium chloride injection, is provided as a premixed, sterile, solution in GALAXY plastic containers and intended for intravenous administration. The drug product is supplied in three strengths, 300 mg/50 mL, 600 mg/50 mL, and 900 mg/50 mL, and contains clindamycin phosphate equivalent to 300 mg, 600 mg, and 900 mg of clindamycin, respectively. Excipients in the proposed formulation include sodium chloride [redacted] (b) (4) adjustment agent and EDTA, [redacted] (b) (4) In addition, sodium hydroxide and/or hydrochloric acid are added to adjust the pH (5.5 – 7.0). The drug product specification includes tests and acceptance criteria for appearance, (clarity, color and particulate matter), pH, osmolality, particulate matter, assay by HPLC, impurities by HPLC, identification by retention time, identification by PDA, sterility, bacterial endotoxin and fill volume. The initially proposed acceptance criteria for pH and osmolality were revised during the NDA review at the FDA recommendations. In addition, several revisions were made to the acceptance criteria for impurities. Specifically, the initially proposed acceptance criteria for two specified impurities [redacted] (b) (4), any unspecified impurity and total impurities were not found to be justified and supported by data submitted in the application, including data generated for the listed drug. The proposed acceptance criteria were discussed in detail with the pharm/tox review team for this NDA [redacted] (b) (4) Following these discussions and exchange of communications with

the Applicant, the initially proposed impurity limits were lowered and a limit for total unspecified impurities was added to the drug product specification. The drug product specification as revised has been found acceptable. The finished drug product is packaged in Baxter's 50 mL single-port PL 2501 Plastic (GALAXY) Container Closure System, which has been previously for a number of other FDA approved injectable products. PL 2501 film is (b) (4) laminate intended for medical solution containers of premixed drug products. Information for the GALAXY containers has been provided via a reference to DMF (b) (4). The suitability and compatibility of the proposed container closure for the current product was assessed during developmental stability studies. Low levels of a leachable compound from the PL 2501 container (b) (4) were found qualified and acceptable by the pharm/tox reviewer. The drug product stability data were submitted for three representative batches of two strengths, 300 mg/50 mL and 900 mg/50 mL, using a bracketing approach and covering the middle strength, 600 mg/50 mL. Based on the overall stability information provided in the initial NDA submission and subsequent amendments (including 18-month stability update submitted for the drug product registration batches stored at 25 deg C/40% RH) and taking into consideration the revised acceptance criteria for impurities, the 18-month expiration dating has been granted for the drug product to be stored at room temperature.

The manufacturing process for the proposed drug product, clindamycin in 0.9% sodium chloride injection, involves manufacturing of a (b) (4) into GALAXY containers using a (b) (4) process. The components in the proposed formulation are highly soluble so the drug product is a true solution. The critical aspects of the manufacturing process include (b) (4) have been found adequate to mitigate potential risks to product quality. Several comments were conveyed to the Applicant during the review and additional information regarding the suitability of the proposed manufacturing equipment, process parameters, and the container closure was provided and found acceptable.

From the product quality microbiology perspective, information provided in the NDA regarding the sterilization validation, drug product specification (endotoxin and sterility) and the container closure integrity was found acceptable.

The Applicant requested a waiver of the requirement to conduct a bioavailability/bioequivalence study (between the proposed and listed drug products) citing 21 CFR § 320.22(b). The request for the biowaiver cannot be granted based on 21 CFR § 320.22(b) due to the difference in the inactive ingredients. However, the FDA can rely on any other approach deemed adequate by FDA to establish the bridge (bioavailability/bioequivalence) between the listed and proposed drug products. Specifically for this NDA, the difference in tonicity adjuster between the formulations of the proposed and the listed drug product is not expected to impact the bioavailability of clindamycin following intravenous administration. Consistent with 21 CFR § 320.24(b)(6) the FDA deems that the bridge (bioavailability/bioequivalence) between the

proposed drug product and the listed drug product is established, and therefore the reliance of this NDA on the Agency's finding of safety and effectiveness of the listed drug is justified.

The clindamycin phosphate drug substance is manufactured by (b) (4) and the drug product is manufactured by Baxter Healthcare Corporation. Based on a review of the application and inspectional documents of the facilities responsible for manufacturing clindamycin in 0.9% sodium chloride injection, no significant outstanding risks were identified. All manufacturing and testing facilities listed in the current NDA and supporting DMFs were found acceptable and an overall "Approve" recommendation was issued by the OPF on April 14, 2017.

C. Special Product Quality Labeling Recommendations (NDA only)
N/A

D. Final Risk Assessment (see Attachment I)

CHAPTERS: Primary Quality Assessment

CHAPTER I: Drug Substance

CHAPTER II: Drug Product

CHAPTER III: Process

CHAPTER IV: Microbiology

CHAPTER V: Biopharmaceutics

CHAPTER VI: Facilities

ATTACHMENT I: Risk Assessment

MICROBIOLOGY

Product Background

NDA: 208083

Drug Product Name / Strength: Clindamycin in 0.9% Sodium Chloride Injection / 300 mg in 50 mL (6 mg/mL), 600 mg in 50 mL (12 mg/mL), and 900 mg (18 mg/mL) in 50 mL, where each is a 50 mL fill in a 50 mL plastic bag (PL 2501 GALAXY), single dos

Route of Administration: Intravenous

Applicant Name: Celerity Pharmaceuticals, LLC

Manufacturing Site:
Baxter Healthcare Corporation
(b) (4)

Method of Sterilization: (b) (4)

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

List Submissions being reviewed (table):

Submit	Received
06/30/16	06/30/16 (SD#4)
10/17/16	10/17/16 (SD#5) [a]
11/04/16	11/04/16 (SD#6) [b]
11/14/16	11/14/16 (SD#7) [c]
02/15/17	02/15/17 (SD#9) [d]

[a] Labeling Amendment, response to Filing Review
[b] Response to Quality IR dated 10/13/16
[c] Response to Quality IR (Microbiology) dated 10/31/16
[d] Response to Quality IR dated 02/08/17, includes revisions in 3.2.P.5 and 3.2.P.8

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

Supporting/Related Documents:
- (b) (4)

- DMF [redacted] (Type III) and corresponding microbiology reviews D6344M03R01.doc and D6344M03R02.doc, 07/27/16 and 09/26/16, Y. Smith – Sterilization processes for container/closure system and [redacted]

Remarks: The subject of review is submitted electronically (eCTD). Some tables in this review are excerpted from the electronic submission. All references to Module, Section, and pdf documents in this review are from the submission dated 06/30/16 except where otherwise noted.

Filename: A208083MR01.docx

S DRUG SUBSTANCE

Reviewer's Assessment: *N/A*

P DRUG PRODUCT

[redacted]

16 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

A.2.4 Viral Clearance Studies

Reviewer's Assessment: *N/A*

R Regional Information

- **Executed Batch Records**

  Executed lot #(s): 71900-71905

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

Reviewer's Assessment: *Adequate*

- **Comparability Protocol** - N/A. The applicant states that no CPs are approved for the GALAXY container or included in this application.

Reviewer's Assessment: *N/A*

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

2.A. Package Insert

Storage temperature: 20-25°C
Route of administration: IV
Container: Single dose

No further dilution and storage instructions are specified in the package insert.

Reviewer's Assessment: *Adequate*

Post-Approval Commitments: N/A

Lifecycle Management Considerations: N/A

List of Deficiencies: N/A

Primary Microbiology Reviewer Name and Date: **Lisa S.G. Shelton, Ph.D., 03/17/2017**

Secondary Reviewer Name and Date (and Secondary Summary, as needed): **Bryan S. Riley, Ph.D., 3/20/2017**

Bryan Riley

Digitally signed by Bryan Riley
Date: 3/20/2017 10:36:15AM
GUID: 503450f200004f5816a1d3ae902b5e91

Lisa Shelton

Digitally signed by Lisa Shelton
Date: 3/20/2017 10:55:45AM
GUID: 508da70c00028f09b2fa2100e27e40a6

BIOPHARMACEUTICS

Product Background:

NDA: 208083

Drug Product Name / Strength: Clindamycin in 0.9% Sodium Chloride Injection; 300 mg/50 mL, 600 mg/50 mL and 900 mg/50 mL

Route of Administration: Intravenous Infusion

Applicant Name: Celerity Pharmaceuticals, LLC

Indication: For the treatment of serious infections caused by susceptible anaerobic bacteria

Review Summary:

NDA 208083, submitted to request an approval of Clindamycin in 0.9% Sodium Chloride Injection for intravenous infusion is a 505(b)(2) submission and relies on NDA 050639 (CLEOCIN PHOSPHATE® in Dextrose 5% in Plastic Container) as the listed drug (LD). The Applicant has submitted a request for a waiver of the requirement to submit in vivo bioavailability/bioequivalence data for the proposed 300 mg/50 mL, 600 mg/50 mL, and 900 mg/50 mL clindamycin in 0.9% sodium chloride injection drug product. The Applicant has submitted the waiver request based on 21 CFR § 320.22(b). This review evaluates the Applicant's request for a waiver of the requirement to submit in vivo bioavailability/bioequivalence data for the proposed product.

Except for the replacement of 5% dextrose with 0.9% sodium chloride, the composition of the proposed product is similar to the listed drug CLEOCIN PHOSPHATE® in Dextrose 5% in Plastic Container (NDA 050639), and has the same strength, dosage form, route of administration, volume, packaging, and dosing regimen. Also the pH and osmolality between the two products are very similar. However, the proposed drug product differs from the listed drug product in that it contains 0.9% sodium chloride rather than 5% dextrose as a tonicity adjuster.

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 by FDA to establish the bridge (bioavailability/bioequivalence) between the listed and proposed drug products. Specifically for NDA 208083, the difference in tonicity adjuster in the formulation of

the proposed drug product is not expected to impact the bioavailability of clindamycin following intravenous administration.

In conclusion, consistent with 21 CFR § 320.24(b)(6) the FDA deems that the bridge (bioavailability/bioequivalence) between the proposed drug product and the listed drug product is established, and therefore the reliance of NDA 208083 on the Agency's finding of safety and effectiveness of the listed drug is justified.

From a Biopharmaceutics perspective, NDA 208083 for Clindamycin in 0.9% Sodium Chloride Injection, 300 mg/50 mL, 600 mg/50 mL and 900 mg/50 mL, is recommended for **APPROVAL**.

List Submissions being reviewed (table):

eCTD sequence #	Received date	Document
0003	06/30/2016	New NDA

Highlight Key Outstanding Issues from Last Cycle: None, this is the first Review Cycle

Concise Description Outstanding Issues Remaining: None

Bridging of Formulations

Reviewer's Assessment: The formulation of the proposed drug product was not changed during the drug product development.

Biowaiver Request

NDA 208083 is a 505(b)(2) submission where Celerity Pharmaceuticals, LLC has requested a biowaiver for the proposed product relying upon NDA 050639 (CLEOCIN PHOSPHATE® in Dextrose 5% in Plastic Container) as the listed drug, citing 21 CFR § 320.22(b). The proposed drug product is a premixed, sterile, nonpyrogenic solution supplied in GALAXY plastic containers and intended for intravenous administration. The drug product is composed of clindamycin phosphate (equivalent to 300 mg/50 mL, 600 mg/50 mL, and 900 mg/50 mL of clindamycin) Sodium Chloride (450 mg/50 mL) and Edetate Disodium Dihydrate (2 mg/50 mL). The pH was adjusted with sodium hydroxide and/or hydrochloric acid (pH range of the final dosage form in 5.5 – 7.0). The solution is packaged in Baxter's 50 mL single-port PL 2501 Plastic (GALAXY) container-closure system and is intended for intravenous use. The

comparative composition of the proposed drug product and the listed drug product is shown in Table 1.

Table 1: Comparative composition of the proposed drug product and the listed drug product

Component	**Proposed product**	**Listed drug product (CLEOCIN PHOSPHATE® in Dextrose 5% in Plastic Container- NDA 050639)**
	Conc. (g/L)	**Conc. (g/L)**
Clindamycin Phosphate, USP	Equivalent to Clindamycin: 6 g/L – 300 mg/50 mL 12 g/L – 600 mg/50 mL 18 g/L – 900 mg/50 mL	Equivalent to Clindamycin: 6 g/L – 300 mg/50 mL 12 g/L – 600 mg/50 mL 18 g/L – 900 mg/50 mL
Edetate Disodium Dihydrate, USP	(b) (4)	0.04
Dextrose Hydrous, USP	-	(b) (4)
Sodium Chloride, USP	9.0	-
Hydrochloric Acid, NF	q.s. for pH adjustment	q.s. for pH adjustment
Sodium Hydroxide, NF	q.s. for pH adjustment	q.s. for pH adjustment
Water for Injection, USP	q.s.	q.s.

Reviewer's Assessment:

As shown in Table 1, the composition of the proposed drug product is the same as the listed drug product, CLEOCIN PHOSPHATE® in Dextrose 5% in Plastic Container, except the dextrose 5% has been replaced with 0.9% NaCl.

Clindamycin phosphate is compatible with sodium chloride, as the package insert for the listed product, CLEOCIN PHOSPHATE® states "Physical and biological compatibility studies monitored for 24 hours at room temperature have demonstrated no inactivation or incompatibility with the use of CLEOCIN PHOSPHATE® Sterile Solution (clindamycin phosphate) in IV solutions containing sodium chloride, glucose, calcium or potassium, and solutions containing vitamin B complex in concentrations usually used clinically." The label states that 6, 9 and 12 mg/mL (equivalent to clindamycin base) in dextrose injection 5%, sodium

chloride injection 0.9%, or Lactated Ringers Injection in glass bottles or minibags, demonstrated physical and chemical stability for at least 16 days at 25°C, 32 days at 4°C, and eight weeks at -10°C. Also the prescribing information for the currently marketed CLEOCIN PHOSPHATE® in ADD-Vantage™ System (NDA 050441) allow for preparation of 600 mg/50 mL or 900 mg/50 mL of CLEOCIN PHOSPHATE® Sterile Solution in 0.9% sodium chloride.

As shown in Table 2, the Applicant has provided comparative data on product assay, osmolality, pH, and total related substances between the proposed product, Clindamycin Injection in 0.9% Sodium Chloride, and the listed product, CLEOCIN PHOSPHATE® IV Solution.

Table 2: Comparison of assay, total impurities, osmolality and pH between the proposed Clindamycin Injection in 0.9% Sodium Chloride after storage for 12 months at Room Temperature (25°C) and the listed drug product, CLEOCIN PHOSPHATE® IV (CLEOCIN PHOSPHATE® in Dextrose 5% in Plastic Container) at expiry

Description	Strength	CLEOCIN PHOSPHATE IV SOLUTION at Expiry (% w/w)	Registration Stability Batches at 25°C for 12 Months (% w/w)
Assay	300 mg	(b) (4)	
	900 mg		
Total Impurities	300 mg		
	900 mg		
Osmolality	300 mg		
	900 mg		
pH	300 mg		
	900 mg		

The assay of the listed drug product was found to be (b) (4)% for the 300 mg strength and (b) (4)% for the 900 mg strength, which were somewhat lower than the assay for the proposed drug product which (b) (4) This could be due to the age of the listed drug product, which is stated to be near the expiration date during the study. Similarly, higher level of impurities ((b) (4)%) were observed in the listed drug product in comparison to (b) (4)% for the proposed drug product, which again could be due to the near expiration date of the listed

drug product at the time of testing. Overall, the assay, total impurity levels, osmolality, and pH were similar between the proposed and listed drug products.

The dosage form, route of administration and dosing regimen for the proposed product are similar to those of the listed drug product. The Applicant has provided a side-by-side comparison between the proposed and the listed drug product, as shown in Table 3.

Table 3. Side-by-side comparison of the proposed and the listed drug product

Parameter	**Listed Drug Product**	**Proposed Drug Product**
Name	CLEOCIN PHOSPHATE® IV Solution (CLEOCIN PHOSPHATE® in Dextrose 5% in Plastic Container)	Clindamycin in 0.9% Sodium Chloride Injection
Active Ingredient	Clindamycin Phosphate	Clindamycin Phosphate
Total Drug Content	300 mg, 600 mg, and 900 mg (as Clindamycin)	300 mg, 600 mg, and 900 mg (as Clindamycin)
Tonicity Adjuster	5% w/v Hydrous Dextrose, USP (b) (4)	0.9% w/v Sodium Chloride, USP (0.45 g/50 mL)
pH Adjuster	Hydrochloric Acid, NF and/or Sodium Hydroxide, NF	Hydrochloric Acid, NF and/or Sodium Hydroxide, NF
Vehicle	(b) (4)	Water for Injection, USP
Volume	50 mL in GALAXY plastic container	50 mL in GALAXY plastic container
Concentration	6 mg/mL, 12 mg/mL, and 18 mg/mL	6 mg/mL, 12 mg/mL, and 18 mg/mL
pH	5.5 – 7.0	5.5 – 7.0
Dosage Form	Injectable: (b) (4), sterile solution (premixed)	Injectable: (b) (4), sterile solution (premixed)
Container Closure System	Single-use plastic container (GALAXY)	Single-use plastic container (GALAXY)
Route of Administration	Injection: Intravenous infusion	Injection: Intravenous infusion
Dosing Regimen	• 300 g dose infusion over 10 minutes • 600 g dose infusion over 20 minutes	• 300 g dose infusion over 10 minutes • 600 g dose infusion over 20 minutes

	• 900 g dose infusion over 30 minutes	• 900 g dose infusion over 30 minutes
Dosing Volume	50 mL	50 mL
Infusion Rate	Should not exceed 30 mg/minute	Should not exceed 30 mg/minute

With the exception of sodium chloride in place of dextrose, the other inactive ingredients in the proposed Clindamycin in 0.9% Sodium Chloride Injection drug product are the same as in the currently marketed listed drug product, CLEOCIN PHOSPHATE® IV Solution (clindamycin injection). All of the proposed strengths will contain 450 mg (0.45 g) of NaCl. Each gram of sodium chloride contains (b) (4) of sodium. Hence the total uptake of sodium per unit dose (50 mL) of Clindamycin in 0.9% Sodium Chloride Injection, 300 mg/50 mL, 600 mg/50 mL or 900 mg/50 mL, will be (b) (4) The FDA recommends a total daily intake of sodium of no more than 2,300 milligrams per day for the general population. The FDA recommends that, in general, individuals with hypertension, blacks, and middle-aged and older adults should limit sodium intake to 1,500 mg per day. Hence, the total amount of sodium intake with the proposed dosage form will be approximately (b) (4)% of the FDA recommended maximum daily intake of sodium for the general population, and approximately (b) (4)% of the FDA recommended maximum daily intake of sodium for the high-risk population.

It is important to note that the name 'CLEOCIN PHOSPHATE®' is used for two different products including CLEOCIN PHOSPHATE® IV Solution (CLEOCIN PHOSPHATE® in Dextrose 5% in Plastic Container) approved under NDA 050639, and CLEOCIN PHOSPHATE® injection approved under NDA 050441. NDA 050639 which is the listed drug for the 505(b)(2) submission of the proposed drug product is administered via the intravenous route. However, CLEOCIN PHOSPHATE® injection approved under NDA 050441 can be administered via the intravenous as well as the intramuscular route. It is important that the label as well as the packaging insert for the proposed product clearly state the route of administration, so that any possible confusion by the patient or the clinical practitioner can be avoided.

The Applicant is requesting a waiver of the requirement to conduct a bioavailability/bioequivalence study (between the proposed and listed drug products) citing 21 CFR § 320.22(b). The request for the biowaiver cannot be granted based on 21 CFR § 320.22(b) due to the difference in the inactive ingredients.

The proposed drug product submitted under a 505(b)(2) NDA does not fully satisfy the criteria for a waiver of evidence of in vivo bioavailability under 21 CFR § 320.22(b)(1). Under this regulation, 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 listed and proposed drug products have the same strength, dosage form, route of administration, dosing regimen, in addition to similar pH and osmolality; however, the proposed drug product differs from the listed drug product in that it contains 0.9% sodium chloride rather than 5% dextrose as a tonicity adjuster.

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 by FDA to establish the bridge (bioavailability/bioequivalence) between the listed and proposed drug products. Specifically for NDA 208083, the difference in tonicity adjuster in the formulation of the proposed drug product is not expected to impact the bioavailability of clindamycin following intravenous administration.

In conclusion, consistent with 21 CFR § 320.24(b)(6) the FDA deems that the bridge (bioavailability/bioequivalence) between the proposed drug product and the listed drug product is established, and therefore the reliance of NDA 208083 on the Agency's finding of safety and effectiveness of the listed drug is justified.

Conclusion and Recommendation

Consistent with 21 CFR § 320.24(b)(6) the FDA deems that the bridge (bioavailability/bioequivalence) between the proposed drug product and the listed drug product is established, and therefore the reliance of NDA 208083 on the Agency's finding of safety and effectiveness of the listed drug is justified.

From the Biopharmaceutics perspective, NDA 208083 for Clindamycin in 0.9% Sodium Chloride Injection for intravenous infusion, 300 mg/50 mL, 600 mg/50 mL and 900 mg/50 mL is recommended for **APPROVAL**.

Primary Biopharmaceutics Reviewer Name and Date:

Kaushalkumar Dave, Ph.D., 01/17/2017
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. Dave's assessment and recommendation.

Elsbeth Chikhale, Ph.D., 01/17/2017
Acting Biopharmaceutics Lead
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

Elsbeth Chikhale

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Kaushalkumar Dave

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Date: 1/17/2017 12:41:55PM
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ATTACHMENT I: Final Risk Assessment

From Initial Risk Identification			Review Assessment		
From Initial Risk Identification	**Review Assessment**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
		H, M, or L		Acceptable or Not Acceptable	
Assay /Stability	Formulation Raw materials Process parameters Scale/equipment Site	M		Acceptable	(b) (4) *(18-month) expiration dating was granted due to* (b) (4)
pH	Formulation Process parameters Scale/equipment Site	L		Acceptable	
Osmolality	Formulation Process parameters Scale/equipment Site	L		Acceptable	
Extractables and leachables	Formulation Container closure	M		Acceptable	*One leachable compound was found acceptable*
Endotoxins	Formulation Raw materials Process parameters Scale/equipment Site	M		Acceptable	
Sterility	Formulation Raw materials	H		Acceptable	

	Process parameters Scale/equipment Site				
Particulate matter	Formulation Raw materials Process parameters Scale/equipment Site	M		Acceptable	

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

Dorota M. Matecka -S

Digitally signed by Dorota M Matecka -S
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Dorota Matecka, Ph.D. ATL for NDA 208083 *on behalf of OPQ Team*