CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215143Orig1s000

PRODUCT QUALITY REVIEW(S)

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U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 215143
Assessment 1

Drug Product Name	Succinylcholine Chloride Solution, Preservative-Free, 100 mg/5 mL
Dosage Form	Solution
Strength	20 mg/mL (100 mg/5 mL)
Route of Administration	intravenous or intramuscular administration
Rx/OTC Dispensed	Rx
Applicant	Hikma Pharmaceuticals USA, Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting document 1; eCTD 0001	1 Oct 20	All, original submission
Supporting document 6; eCTD 0006	14 Jan 21	biopharm
Supporting document 9; eCTD 0009	8 Mar 21	Biopharm, process/manufacturing, drug product
Supporting document 11; eCTD 0011	6 Apr 21	Process/manufacturing
Supporting document 12; eCTD 0012	8 Apr 21	Microbiology
Supporting document 13; eCTD 0013	24 May 21	Microbiology
Supporting document 14; eCTD 0014	1 Jun 21	Drug product
Supporting document 15; eCTD 0015	24 Jun 21	Drug product
Supporting document 16; eCTD 0016	30 Jun 21	Drug product
Supporting document 17; eCTD 0017	8 Jul 21	Drug Product

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Katie Duncan	Donna Christner
Drug Product	Jizhou Wang	Julia Pinto
Manufacturing	Khalid Khan	Frank Wackes
Microbiology	Karthik Krishnan	Yeissa Chabrier-Rosello
Biopharmaceutics	Kamrun Nahar	Hansong Chen
Regulatory Business Process Manager	Anika Lalmansingh	
Application Technical Lead	Valerie Amspacher	
Laboratory (OTR)	N/A	N/A
Environmental	Jizhou Wang	Julia Pinto

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

CMC recommends approval of this application based on drug substance, drug product, process/manufacturing, biopharmaceutics and microbiology reviews.

A shelf-life of 15 months is acceptable when stored refrigerated (2-8˚C). The pre-filled syringes may be stored for up to 14 days at (b) (4) room temperature.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Succinylcholine Chloride Solution, Preservative-Free, is packaged in one configuration as a 5 mL fill (20 mg/mL concentration (100 mg/5 mL)) in a 5 mL single dose prefilled syringe (PFS).

A shelf-life of 15 months is acceptable when stored refrigerated (2-8˚C). The pre-filled syringes may be stored for up to 14 days at (b) (4) room temperature.

USP definition of refrigerated - Refrigerator: A cold place in which the temperature is controlled between 2° and 8° (36° and 46° F).

(b) (4)

(b) (4)

Proposed Indication(s) including Intended Patient Population	adjunct to general anesthesia, to facilitate tracheal intubation, and to provide skeletal muscle relaxation during surgery or mechanical ventilation
Duration of Treatment	acute
Maximum Daily Dose	600 mg
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance CMC information for succinylcholine chloride is cross referenced to DMF (b) (4)
The applicant provides a brief description of the general properties of the drug substance and impurities. The applicant provides a drug substance specification that is in accordance with the USP and the drug substance manufacturer. The applicant provided details on the tests performed upon acceptance of drug substance from the supplier and method verification data are provided. The drug substance manufacturer proposes a retest period of (b) (4) months, which is acceptable based on the stability data provided in the cross-referenced DMF.

Drug Product: Adequate

The release specifications of the drug product have been adequately controlled. The suitability of the container closure system (CCS) PFS was validated by long-term and accelerated stability and photostability studies and extractables and leachables studies.
The combined extractables from the assembled PFS extraction and the CES on individual components can be deemed a complete extractable profile for the CCS, and the profile can represent the worst scenario of the leachables. All the detected leachables from the 0, 12, and 18 M stability samples are corelated with extractable studies and thus a good Extractables/Leachables correlation was established.
The stability specifications have wider acceptance criteria for significant metabolites Succinylmonocholine Chloride and Choline Chloride, and Total Degradation Products (including (b) (4)) than those of release specifications. The wider acceptance criteria for such impurities have been justified by the inhouse data trend and RLD impurity profiles.
Three (3) registration batches with both upright and horizontal (a justified

worst scenario) orientations have been placed for stability studies under accelerated conditions of 25 ± 2°C /60 ± 5% RH and long-term stability condition of 5˚C.
The Sponsor proposed a shelf life of 15 months for the drug product at refrigerated temperature based on the statistical evaluations. Supporting stability data of Photostability Study, Freeze-Thaw Study, Fourteen Day Room Temperature Study and In-use/diluent studies have been provided to support the stability profiles for use and shipping.

Labeling: Adequate

Manufacturing: Adequate

The manufacturing process consists of (b) (4) (b) (4) (b) (4) The data reported on the exhibit batches support the proposed manufacturing process for scaled up batch size. The manufacturing instructions, manufacturing equipment, environmental controls, in-process controls and controls for the (b) (4) are adequate to support manufacture of succinylcholine chloride injection in pre-filled syringes for this application.
The drug product manufacturing facility Hikma Pharmaceuticals USA, Inc. (FEI 2220525), the drug substance manufacturing facility (b) (4) (b) (4) and the test facility (b) (4) (b) (4) maintain adequate compliance status.

Biopharmaceutics: Adequate

The only difference between the proposed drug and the Listed Drug (LD) is the absence of methylparaben and propylparaben in the proposed drug which act as the preservatives in the formulation of the LD.
Q1/Q2 analysis showed that the proposed product is Q1/Q2 the same as the LD product. The Applicant provided adequate justification for the sameness of the proposed drug product and the LD product. The physicochemical property data between the proposed and listed drug products are comparable. Therefore, as per the 21 CFR 320.22(b)(1), the biowaiver can be granted for the proposed drug product.

Microbiology (if applicable): Adequate

Method of Sterilization: (b) (4) (b) (4) (b) (4) has been adequately validated.

The applicant has met regulatory expectations with regard to the test method, acceptance criteria and verification of the suitability of use of the sterility test that will be performed on the drug product prior to its release.

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations / Comments**
		H, M, or L		Acceptable or Not Acceptable	
Sterility	• Formulation • Container closure • Process parameters • Scale/ equipments • Site	H	Manufacturing process / specification	Acceptable	
Endotoxin Pyrogen	• Formulation • Container closure • Process parameters • Scale/ equipments • Site	M	Manufacturing process / specification	Acceptable	
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L	Specification	Acceptable	
Uniformity of Dose (Fill Volume/deliverable volume)	• Formulation • Container closure • Process parameters • Scale/equipments • Site	L	Specification	Acceptable	
Osmolality	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L	Specification	Acceptable	

pH- (Low)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L	Specification	Acceptable	
Particulate matter (non aggregate for solution only)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	M	Specification	Acceptable	
Leachable extractables	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L	Determined by original review to be acceptable, no further testing required	Acceptable	
Appearance (Color/ turbidity)	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L	Specification	Acceptable	

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

2. Drug Substance Deficiencies

3. Drug Product Deficiencies

4. Labeling Deficiencies

5. Manufacturing Deficiencies

6. Biopharmaceutics Deficiencies

7. Microbiology Deficiencies

8. Other Deficiencies (Specify discipline, such as Environmental)

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	1	8 Apr 20	Wei Song
	III			4		
	III			4		
	V			4		
	III			4		
	III			4		
	III			4		

Action codes for DMF Table:
1 – DMF Reviewed.
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application

5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
ANDA	213229	Hikma's ANDA for this drug product (b) (4)
NDA	008845	Quelicin, owned by Hospira

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH-ODE				
CDRH-OC				
Clinical				
Other				

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	N/A	N/A
Established name(s)	SUCCINYLCHOLINE CHLORIDE	Adequate
Route(s) of administration	intravenous	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	5 mL Succinylcholine chloride injection, USP prefilled syringe 20 mg/mL (100 mg/5mL)	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	single dose	Adequate

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		

Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	**Compatibility and Admixtures** (b) (4) [redacted] **Risk of Medication Errors** Accidental administration of neuromuscular blocking agents may be fatal. Store succinylcholine chloride injection with the syringe tip cap intact and in a manner that minimizes the possibility of selecting the wrong product. **Instructions for Use of Prefilled Syringe** CAUTION: Assure that the needle or Needleless Luer Access Device (NLAD) is securely attached before beginning the injection. Visually inspect the syringe-needle or syringe-NLAD connection before and during drug administration.	Adequate

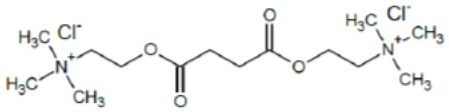
1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Injection	Adequate
Strength(s) in metric system	5 mL prefilled syringe (100 mg/5mL)	Adequate

If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	FDA salt rule does not apply since the RLD was approved in 1953	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	No	No Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	No. did not include " single-dose"	No Adequate

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Succinylcholine Chloride Injection, USP	Adequate
Dosage form(s) and route(s) of administration	a sterile, nonpyrogenic solution for intramuscular (IM) or intravenous (IV) use.	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	FDA salt rule does not apply since the RLD was approved in 1953	Adequate
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Not provided	Inadequate
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Not provided	Inadequate
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Statement of being sterile (if applicable)	Yes	Adequate
Pharmacological/therapeutic class	depolarizing skeletal muscle relaxant	Adequate

Chemical name, structural formula, molecular weight	Ethanaminium, 2,2'-[(1,4-dioxo-1,4-butanediyl) bis(oxy)]bis[*N, N, N*-trimethyl-, dichloride, dihydrate,  Molecular formula: C14H30Cl2N2O4•2H2O Molecular weight: 397.34.	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa or pH)	pH is 3.6 (3.0 to 4.5).	Adequate

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	N/A
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	N/A

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Prefilled Syringe	Adequate
Strength(s) in metric system	20 mg/mL, 5 mL	Adequate
Available units (e.g., bottles of 100 tablets)	5 mL single-dose prefilled syringes packaged in a carton of 10.	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	NDC # 0143-6234-10	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package	Single-dose	Adequate

terms include pharmacy bulk package and imaging bulk package.		

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	**Store in refrigerator 2° to 8°C (36° to 46°F).** The single-dose syringes are stable for up to 14 days at room temperature without significant loss of potency.	Adequate
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	Adequate
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store in refrigerator 2° to 8°C (36° to 46°F).	Adequate
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	Not provided	Inadequate
Include information about child-resistant packaging	N/A	N/A

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Manufactured by:	Hikma Pharmaceuticals USA Inc. Berkeley Heights, NJ 07922	Adequate

2.0 PATIENT LABELING

N/A

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CARTON AND CONTAINER LABELING

3.1 & 3.2. Container and Carton Label

Container label:

(b) (4)

(b) (4)

Cartoon label

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	yes	Adequate
Dosage strength	yes	Adequate
Route of administration	yes	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	FDA salt rule does not apply since the RLD was approved in 1953	Adequate
Net contents (e.g. tablet count)	yes	Adequate
"Rx only" displayed on the principal display	yes	Adequate
NDC number	yes	Adequate
Lot number and expiration date	yes	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	yes	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	yes	Adequate
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	Adequate

If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Bar code	Yes	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Yes	Adequate
Medication Guide (if applicable)	yes	Adequate
No text on Ferrule and Cap overseal	N/A	N/A
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	N/A
And others, if space is available	N/A	N/A

Assessment of Carton and Container Labeling: ***Inadequate***

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

ITEMS FOR ADDITIONAL ASSESSMENT

a. In Section3, include a description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, and provide single-dose labeling term.
b. In Section 11, list names of all inactive ingredients. Use USP/NF names. Avoid Brand names. And include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.
c. 1in Section 16, if product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."

Overall Assessment and Recommendation:

Not adequate

Primary Labeling Assessor Name and Date:
Secondary Assessor Name and Date (and Secondary Summary,

APPEARS THIS WAY ON ORIGINAL

APPEARS THIS WAY ON ORIGINAL

Jizhou Wang

Digitally signed by Jizhou Wang
Date: 7/11/2021 10:09:56PM
GUID: 53160853000083c4052c25f3a3cf964a

Julia Pinto

Digitally signed by Julia Pinto
Date: 7/12/2021 11:39:09AM
GUID: 5050dbcb00001294a888a4bdc20a3a58

BIOPHARMACEUTICS

Product Background: Hikma Pharmaceuticals USA, Inc. developed Succinylcholine Chloride Injection, 100 mg/5 mL (20 mg/mL) Pre-Filled Syringes referencing Quelicin® injection, 20 mg/mL (200 mg in 10 mL vial), approved under NDA 008845 held by HOSPIRA INC. Succinylcholine chloride is indicated as an adjunct to general anesthesia, to facilitate tracheal intubation, and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

NDA: 215143

Drug Product Name / Strength: Succinylcholine Chloride Injection, USP, 100 mg/5 mL (20 mg/mL) Pre-Filled Syringes

Route of Administration: Intravenous and Intramuscular

Applicant Name: Hikma Pharmaceuticals USA, Inc.

Primary Reviewer: Kamrun Nahar, PhD

Secondary Reviewer: Hansong Chen, PharmD, PhD

Review Recommendation: **Adequate**

Review Summary:
The Applicant developed Succinylcholine Chloride Injection, USP, 100 mg/5 mL (20 mg/mL) Pre-Filled Syringes (PFS) which is ready to-be used. This is a 505(b)(2) application and the listed drug (LD) is Quelicin® (Succinylcholine Chloride) Injection, USP 200 mg/10 mL (20 mg/mL) packaged as multiple-dose vial approved under NDA 008845. The Applicant requested a biowaiver for their proposed drug product by citing 21 CFR320.22(b)(1).

The proposed drug product Succinylcholine Chloride Injection, USP, 100 mg/5 mL (20 mg/mL) Pre-Filled Syringes (PFS) is clear, colorless solution which is preservative free. The only difference between the proposed drug and the LD is the absence of methylparaben and propylparaben in the proposed drug which act as the preservatives in the formulation of the LD. The composition of the proposed drug product is given below:

Table 1: Composition of the proposed Succinylcholine Chloride Injection, USP, 100 mg/5 mL (20 mg/mL) Pre-Filled Syringes

Succinylcholine Chloride Injection, USP Preservative Free 20 mg/mL, 5 mL PFS					IID %w/v
Component	Function	Amount per mL	Amount per PFS	Unit (% w/v)	
Succinylcholine Chloride, USP	Active	20 mg	100 mg	1.0%	N/A
Sodium Chloride, USP	Isotonicity Agent	4.5 mg	22.5 mg	0.225%	14%
Hydrochloric Acid, NF (as 1N solution)	pH adjuster	To adjust pH to 3.0 to 4.5			ADJ PH
[redacted] (b) (4)					

Solubility:
Succinylcholine chloride is highly soluble across the physiological pH range which is given below:

Table 2: Solubility of Succinylcholine Chloride across the physiological pH range 1.2 to 6.8

Buffer pH	Solubility in mg/mL
1.2	379.35
4.5	505.43
6.8	477.53
Water	509.26

Biowaiver request:

The Listed Drug (LD) and the proposed drug product have differences in their composition, i.e. the LD drug has methylparaben and propylparaben as preservatives in its formulation while the proposed drug is preservative free. The Applicant requested a biowaiver for their proposed drug product as per the 21 CFR 320.22(b)(1).

The Applicant provided the following justifications:

a. The proposed drug product and the LD product are solutions which are 100% bioavailable.
b. The proposed drug product and the LD product are intended to be administered through the same routes, i.e. intravenous and intramuscular.
c. The proposed drug product and the LD product contain the same concentration of active pharmaceutical ingredient. The proposed drug product is preservatives free. The proposed drug product used sodium chloride, [redacted] (b) (4), and hydrochloric acid to adjust the tonicity; and the pH range of the drug product is pH 3.0 to 4.5 which are also present in the LD product. Based on the isotonicity information mentioned in the packaging insert and using the Applicant's prior knowledge during the development of the ANDA 213229, the Applicant experimentally determined the amount of NaCl, [redacted] (b) (4) and hydrochloric acid, and found their proposed drug product was qualitatively (Q1)/quantitively (Q2) the same as the LD product. This Reviewer also assessed

quantitative sameness of NaCl between the proposed drug and LD and found that NaCl is less than (b) (4) in the proposed formulation, indicating Q2 sameness of NaCl. The LD did not mention the amount of sodium hydroxide and hydrochloride to adjust pH (pH 3.0 to 4.5). Hence, the amount could not be determined.

d. The LD product contains methyl paraben and propylparaben as the preservatives. However, the proposed drug product does not contain any preservatives. The Applicant stated that the absence of preservatives does not have any impact on the in vivo performance of the proposed product due to the following reasons:
   - Succinylcholine Chloride is used as an adjunct to the general anesthesia, to facilitate tracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation. No literature is indicating that methyl- and propyl- paraben have similar mechanism of action.
   - Neither parabens (i.e. methyl- and propyl- paraben) do accumulate in human tissue nor modulate liver metabolism to interfere with the metabolism or pharmacology of succinylcholine chloride. Therefore, it is believed that the absence of paraben preservatives has any impact of the pharmacokinetic properties of the proposed preservative-free drug products.
   - Per the CFR 314.94(a)(9)(iii), the removal of preservatives is acceptable from the drug product for parenteral use. Preservatives are considered as "exception excipients". Thus, the removal of the parabens does not affect the safety and efficacy of the proposed drug product.

e. The physicochemical properties of the proposed product and LD are comparable. The Applicant provided physicochemical properties, pH, osmolality and viscosity values of initial (T0), 3 months (3M) and 6 months (6M) time periods. The pH and viscosity of the proposed drug and LD are similar. However, the osmolality of the proposed drug product is slightly lower than the LD product which is believed not to have any impact on the safety and bioavailability. The comparative physicochemical properties of the proposed drug and LD are given below:

Table 3: Comparative physicochemical properties of the proposed Succinylcholine Chloride injection and the LD product.

Table 1 Test Results for Hikma and Reference Products						
	Hikma Submission Batch (Preservative Free)			Reference Products		(b) (4)
	P029412	P029387	P029385	Hospira RLD Lot: 14313EV Expiration: 05/01/2021	Hospira RLD Lot: 14304EV Expiration: 05/01/2021	
pH	3.7 (T0) 3.5 (3M) 3.5 (6M)	3.8 (T0) 3.5 (3M) 3.5 (6M)	3.8 (T0) 3.5 (3M) 3.5 (6M)	3.6 3.6 3.6	3.5 3.5 3.5	
Osmolality (mOsm/kg)	281 279 282	280 281 280	281 279 282	301 301 301	300 300 300	
Viscosity at 25°C (cP)	1.1 1.1 1.1	1.1 1.1 1.1	1.1 1.1 1.1	1.1 1.1 1.2	1.1 1.2 1.1	

Reviewer's assessment:
The LD and the proposed drug product contain same excipients except for the preservatives. The composition of the Quelicin®, the LD product is given below:

Table 4: Quantitative composition of Quelicin® (Succinylcholine Chloride Injection, USP) 20 mg/mL, 10 mL (LD product)

Component	Quantity per Milliliter (mL)	**Strength:** 20 mg/mL 200 mg/10mL **Quantity per unit**
(b) (4)	20 mg	200 mg
Quelicin Chloride (Succinylcholine Chloride, USP) (b) (4)	22.65 mg	226.5 mg
(b) (4)		
Methylparaben, NF (b) (4)	1.8 mg	18 mg
Propylparaben, NF (b) (4)	0.2 mg	2 mg
Sodium Chloride, USP	4.65 mg	46.5 mg
Sodium Hydroxide, NF, (b) (4)	(b) (4)	
Hydrochloric Acid, NF		
Water for Injection, USP		(b) (4)

q.s. = Quantity sufficien[1] (b) (4) The final pH range of the finished drug product is (b) (4)

Note: In the LD product, (b) (4)

Table 5: Qualitative (Q1)/quantitative (Q2) sameness of the proposed and LD product

Component	LD (mg/mL)	Proposed product (mg/mL)	%Differences
Succinylcholine Chloride (API)	20	20	N/A
Methylparaben (preservative)	1.8	Absent	N/A
Propylparaben (preservative)	0.2	Absent	N/A
Sodium Chloride (b) (4)	4.65	4.5	(b) (4)
Sodium Hydroxide (pH adjuster)	q.s.	(b) (4)	
Hydrochloric Acid (pH adjuster)	q.s.	q.s.	N/A

Water for injection (vehicle)	q.s.	(b) (4)

(b) (4)

q.s.: Quantity sufficient

N/A: Not applicable

Succinylcholine Chloride is a highly soluble compound and the proposed drug product is a solution and preservative free. The LD and the proposed drug product are containing the same concentration of active ingredient. The amount of the inactive ingredients, i.e. sodium chloride and hydrochloric acid and/or sodium hydroxide which could not be determined as the LD label did not mention the amount of these active ingredients. Q1/Q2 analysis showed that the proposed product is Q1/Q2 the same as the LD product. The Applicant provided adequate justification for the sameness of the proposed drug product and the LD product. The physicochemical property data between the proposed and listed drug products are comparable. Therefore, as per the 21 CFR 320.22(b)(1), the biowaiver can be granted for the proposed drug product.

Conclusion and Recommendation

From a Biopharmaceutics perspective, this Reviewer concludes that NDA 215143 for Succinylcholine Chloride Injection, USP, 100 mg/5 mL (20 mg/mL) Pre-Filled Syringes is **adequate for approval** as per the 21 CFR.320.22(b)(1).

List Submissions being reviewed:

Submission Date	Purpose of Submission
10/01/2020	0001 (1) ORIG-1/Multiple categories/Subcategories
03/08/2021	0009 (9) ORIG-1/Quality/Response

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

Reviewer's Assessment: ***Adequate.***

Appendix 1

(b) (4)

Kamrun Nahar

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Hansong Chen

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	215143
Assessment Cycle Number	01
Drug Product Name/ Strength	Succinylcholine Chloride Injection, USP / 20 mg/mL (100 mg/5 mL Pre-Filled Syringes)
Route of Administration	Intramuscular (IM) and Intravenous (IV)
Applicant Name	Hikma Pharmaceuticals USA, Inc.
Therapeutic Classification/ OND Division	CDER/ON/DAAP
Manufacturing Site	Hikma Pharmaceuticals USA, Inc. 2 Esterbrook Lane Cherry Hill, NJ 08003-4099
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary:

List Submissions being assessed (table):

Document(s) Assessed	Date Received
eCTD seq#0001	10/01/2020
eCTD seq#0009	03/08/2021
eCTD seq#0012	04/08/2021
eCTD seq#0013	05/24/2021

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: This NDA is for Succinylcholine Chloride Injection, USP (20 mg/mL) is indicated as an adjunct to general anesthesia, to facilitate tracheal intubation, and to provide skeletal muscle relaxation during surgery or mechanical ventilation. The drug product (100 mg/5 mL Pre-Filled Syringe) is sealed with a ready-to-use (b) (4) closure and a (b) (4) plunger rod. The firm references approved Succinylcholine Chloride Injection, USP, 20 mg/mL preserved vial drug product currently marketed under ANDA 213229. This review includes information requests sent on 03/09/2021 and responses received on 04/08/2021.

Concise Description of Outstanding Issues: None

Supporting Documents:

(b) (4)

S DRUG SUBSTANCE

The drug substance is not provided sterile. Therefore, a product quality microbiology review of the drug substance is not reviewed.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Section 3.2.P.1, pg. 1/1 in "description-and-composition.pdf"

The proposed drug product, Succinylcholine Chloride Injection, USP is a clear, colorless, preservative-free solution free of visible particles presented as a single dose prefilled syringe (PFS) with 5 mL fill (20 mg/mL).

Drug product composition

Ingredient	Quantity per mL	Function
Succinylcholine Chloride, USP	20 mg	Active ingredient
Sodium Chloride, USP	4.5 mg	Isotonicity agent
Hydrochloric Acid, NF	q.s. to pH 3.0-4.5	pH adjuster

(b) (4)

Description of container closure system

Section 3.2.P.7, pgs. 1-6/6 in "container-closure-system-narrative.pdf"

Component	Description	Manufacturer
Barrel syringe with tip cap (primary)	(b) (4)	
Plunger stopper (primary)		
Plunger rod (no product contact)		
Clear overwrap (secondary)		

The commercial packaging configuration includes 10 labeled syringes in a shelf carton with 1 piece of package insert labeling.

Assessment: *Adequate*

The applicant provided an adequate description of the drug product's composition and container closure system.

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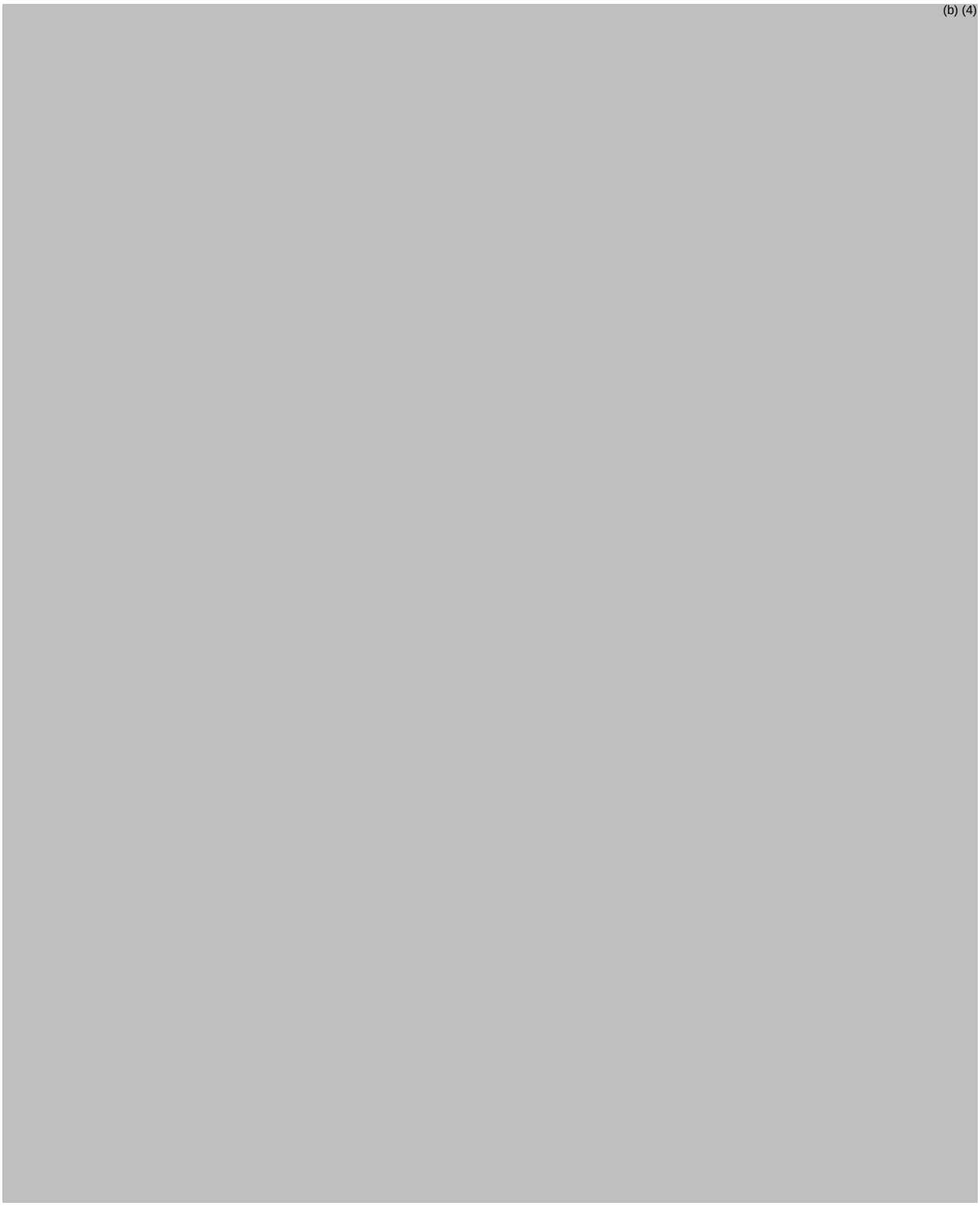

P.7 CONTAINER CLOSURE - See P.1.

P.8 STABILITY

P.8.1 STABILITY SUMMARY AND CONCLUSION

Section 3.2.P.8.1, pg. 1/1 in "stability-summary-narrative.pdf"

Stability protocol includes long term (5±3 ºC) and accelerated (25±2 ºC/60±5% RH) stability studies. The following three exhibit batches were covered under the proposed stability protocol: P029385, P029387, and P029412.

Proposed Expiry: 15 months at 2-8 °C

Applicant notes that the expiration date may be extended based upon long-term stability data from three commercial lots.

Additionally, the proposed label provides for storage for up to 14 days at room temperature after removal from refrigeration (*see section 3.2.P.8.3, pg. 3/3 in "stability-data-narrative.pdf"*). The firm provided a room temperature study to support this provision. However, the study did not include any microbiological tests.

Assessment: *Adequate*
The label provides for storage for up to 14 days at room temperature after removal from refrigeration. However, this storage provision is for unopened syringe. Therefore, the CCIT testing results suffice to assure microbiological quality. No additional microbiological testing is necessary. The applicant has met regulatory expectations with regard to the proposed expiration date.

P.8.2 POST-APPROVAL STABILITY PROTOCOL AND STABILITY COMMITMENT
Section 3.2.P.8.2, pg. 2/3 in "postapproval-stability-pv6161a.pdf"

The microbial specification for product stability are the same as the release specification.

The testing schedule in the post-approval protocol is as follows:
Stability storage conditions: 2-8 °C

Test	Time (Months)						
	0	3	6	9	12	15	18
Bacterial Endotoxins	X				X	X	X
Sterility	X					X	X

Post Approval Stability Commitment
Section 3.2.P.8.2, pg. 1/1 in "postapproval-stability-commitment.pdf"

The applicant commits to placing the first three commercial lots of the subject drug product into their stability program. Thereafter, on an annual basis, at least one production lot will be added to the stability program.

Assessment: *Adequate*

The applicant has met regulatory expectations with regard to the design of the stability testing program to support the drug product's microbiological quality throughout its shelf life.

P.8.3 STABILITY DATA
Seq #0012, section 3.2.P.8.3, pgs. 3-33/34 in "stability-data-gtr52825v3.pdf"

Data for three exhibit batches (P029385, P029387, and P029412) is available for up to 15 months at long-term storage conditions and 6 months at accelerated storage conditions. For sterility testing, all three exhibit batches were marked "sterile" in both horizontal and upright storage positions for 3 and 6 -month time points of accelerated storage as well as 12 and 15 -month time points of long-term storage. For bacterial endotoxin testing (specification: NMT (b) (4)), all three exhibit batches were marked "NMT (b) (4)" in both horizontal and upright storage positions for 3 and 6 -month time point of accelerated storage as well as 12 and 15 -month time points of long-term storage. However, the firm notes that the bacterial endotoxin result was contemporaneous with the specification and testing method that existed at that time and that the actual result is (b) (4) which is below the currently proposed revised specification.

Assessment: *Adequate*
The stability data submitted to date support the microbiological quality of the subject drug product.

R REGIONAL INFORMATION

Executed Batch Records

Executed lot #(s) and corresponding document reference in section 3.2.R:
#P029385 - "reg-info-p029385b.pdf" (25 pgs.), "reg-info-p029385c.pdf" (481 pgs.)
#P029387 - "reg-info-p029387b.pdf" (11 pgs.), "reg-info-p029387c.pdf" (193 pgs.)
#P029412 - "reg-info-p029412b.pdf" (24 pgs.), "reg-info-p029412c.pdf" (207 pgs.)

The batch records confirm that validated sterilization process was used for the manufacture of the exhibit batches.

Assessment: *Adequate*
The applicant has met the regulatory expectations regarding the executed batch records.

Comparability Protocols - No CP was included in the application.

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

2.A. Prescribing Information

Post-dilution/constitution hold time

Section 1.14.1.3, pgs. 4-6/18 in "draft-labeling-text.pdf"

Storage temperature: 2-8 °C
Maximum storage time: 15 months

- The proposed label notes that the single-dose syringes are stable for up to 14 days at room temperature without significant loss of potency.

Route of administration: Intravenous (IV) and Intramuscular (IM)
Container: Single dose pre-filled syringe
Reconstitution: No reconstitution indicated.
Further product dilution: The firm noted that the subject drug product could be used in admixtures of 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP for intravenous infusion (*see section 3.2.P.8.3, pg. 3/3 in "stability-data-narrative.pdf"*). However, the diluents (5% Dextrose or 0.9% Sodium Chloride) for these admixtures are not indicated in the draft label. Microbiological studies were performed to validate the post-dilution storage time of (b) (4) hours at (b) (4) (*see section 3.2.P.2, pgs. 4-15/15 in "pharmaceutical-development-20-123.pdf"*).

Exhibit batch #P029385 was used for the in-use study. The test sample (25 mL) was diluted in IV bag diluents (500 mL of 0.9% Sodium Chloride Injection USP or 5% Dextrose Injection USP) to a final concentration of 1 mg/mL. The admixtures were challenged with five compendial organisms as listed in USP<51> at 10-100 cfu per mL of the admixture. Positive controls without the drug product and negative controls without the inoculum were utilized to validate the assay. The test and control admixtures were then incubated at 20-25 °C and samples were removed at 0, 6, 24, 30 and 48 hours to determine increase, if any, of microbial content in the admixtures during the storage period. The microbial enumeration was carried out on TSA plates incubated at 30-35 °C for 2-4 days or SDA plates that were incubated at 20-25 °C for 3-5 days (2-4 days for *Candida albicans*).

Acceptance criteria: NMT (b) (4)

Results: Microbial growth in both admixtures met the acceptance criterion. All microorganisms tested showed NMT (b) (4) in both admixtures. No growth was observed in any of the negative controls. Positive controls showed growth, with higher growth of the challenge organisms in 0.9% saline than in 5% Dextrose. The results are summarized in table below:

Challenge organism	Log_{10} of microbial recovery count									
	Test					Positive control				
	0 h	6 h	24 h	30 h	48 h	0 h	6 h	24 h	30 h	48 h
5% Dextrose										
Staphylococcus aureus	1.85	1.61	0.48	0.30	N/A	1.71	1.38	N/A	N/A	N/A
Pseudomonas aeruginosa	1.20	0.48	N/A	N/A	N/A	1.15	0.00	N/A	N/A	N/A
Escherichia coli	1.83	1.54	1.11	0.85	N/A	1.83	1.49	1.15	0.85	N/A

Candida albicans	1.34	1.26	0.78	0.90	0.48	1.30	1.23	0.90	0.90	1.18
Aspergillus brasiliensis	1.41	1.36	1.60	1.46	1.26	1.40	1.32	1.45	1.43	1.38
0.9% Saline										
Staphylococcus aureus	1.75	1.59	0.30	N/A	N/A	1.79	1.75	1.38	0.78	0.00
Pseudomonas aeruginosa	1.45	N/A	0.95	1.04	0.00	1.48	1.46	1.30	1.18	0.95
Escherichia coli	1.90	1.74	1.67	1.63	1.61	1.91	1.73	1.62	1.78	1.65
Candida albicans	1.32	1.32	1.04	1.20	1.30	1.41	1.11	1.26	1.11	1.28
Aspergillus brasiliensis	1.45	1.26	1.11	1.23	1.45	1.36	1.36	1.26	1.58	1.38

Assessment: *Adequate*
The firm has adequately validated in-use stability of the diluted drug product and has met regulatory expectations with regard to the information related to product quality microbiology.

Post-Approval Commitments – None

MICROBIOLOGY LIST OF DEFICIENCIES

None

Primary Microbiology Assessor Name and Date: Karthik Mosur Krishnan, Ph.D., Primary reviewer, 05/26/2021

Secondary Assessor Name and Date: Yeissa Chabrier Rosello, Ph.D., Senior Pharmaceutical Quality Assessor, 05/26/2021

Karthik Krishnan

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