CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215143Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	215143
Supporting document/s:	SDN 1, 10/01/2020; SDN 6, 01/14/2021
Applicant's letter date:	October 01, 2020
CDER stamp date:	October 01, 2020
Product:	Succinylcholine Chloride Injection, USP, Preservative-Free; 100 mg/5 mL (20 mg/mL) Pre-Filled Syringes
Indication:	As an adjunct to general anesthesia, to facilitate tracheal intubation, and to provide skeletal muscle relaxation during surgery or mechanical ventilation
Applicant:	Hikma Pharmaceuticals USA Inc.
Clinical Review Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Reviewer:	Imran M. Khan, PhD
Supervisor:	Jay H. Chang, PhD
Deputy Director:	R. Daniel Mellon, PhD
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Project Manager:	Sandy Truong, PharmD

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1 Executive Summary

1.1 Introduction

NDA 215143 was submitted to seek marketing approval for Succinylcholine Chloride Injection, USP 20 mg/mL, as an adjunct to general anesthesia, to facilitate tracheal intubation, and to provide skeletal muscle relaxation during surgery or mechanical ventilation. The NDA was submitted as a 505(b)(2) application relying on the Agency's previous finding of safety and efficacy of the listed drug QUELICIN™ (succinylcholine chloride injection, USP) approved under NDA 008845 for Hospira, Inc. The approved products under the referenced NDA, QUELICIN is indicated for the same indication as described above.

1.2 Brief Discussion of Nonclinical Findings

No new nonclinical toxicological studies were submitted with the NDA.
Drug substance impurities and drug product degradants are either within specification limits according to the ICH Q3A(R2) and Q3B(R2) guidances, respectively, or their levels can be justified to be safe for human use based on the levels being within the approved referenced product.

Extractables and leachables studies were performed to justify the safety of the proposed container closure system, which consists of a 5 mL prefilled plastic syringe with plastic tip cap, plunger stopper, plunger rod, and adhesive label. Although numerous potential leachables including elemental impurities were identified in the extractables study with the container closure system, only two organic compounds (b) (4) (b) (4) and 2 USP <232> elemental leachables ((b) (4)) were found in the long-term stability sample at or above the Applicant's reporting limit of (b) (4) mcg/mL. The levels of (b) (4) are not of human safety concern as the permissible daily exposure (PDE) levels for these leachables are higher than the maximum daily intake (MDI) that patients could be exposed to via administration of the drug product at the maximum recommended daily dose. Although there are no toxicological data for (b) (4) to determine the PDE for this leachable, QSAR analysis both by the Applicant and the Agency find it to be non-mutagenic. Moreover, analysis of the toxicological data available for appropriate surrogate compounds for (b) (4) provide PDEs that indicate that MDI of (b) (4) mg/day for the leachable impurity does not present a safety concern for humans with the parenteral administration of the drug product. Therefore, we have no safety concern regarding potential leachables arising from the container closure system.

In addition, the Applicant provided (b) (4)
(b) (4)

1.3 Recommendations

1.3.1 Approvability

From a nonclinical perspective, the NDA may be approved. However, the proposed labeling might require further discussion among the nonclinical, clinical, and maternal health review teams before a final labeling revision is recommended.

1.3.2 Additional Non Clinical Recommendations

N/A

1.3.3 Labeling

The Applicant's proposed label language is shown in the 2nd column (from left) of the table below. The right columns summarize this reviewer's recommended changes, rationale for this reviewer's recommended changes and general comments. The final label, which will be based on further internal discussion and negotiations with the Applicant, can be found in the Action letter.

Listed Drug (QUELICIN) Labeling	Applicant's Proposed Labeling	Recommended Changes to Proposed Labeling	Rationale for recommended changes/Comment
(b) (4)			

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(b) (4)

2 Drug Information

2.1 Drug

CAS Registry Number: 6101-15-1

Generic Name: Succinylcholine Chloride

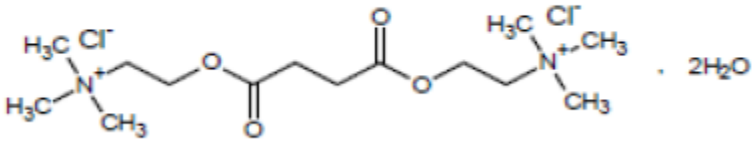
Code Name: N/A

Chemical Name: Ethanaminium, 2,2'-[(1,4-dioxo-1,4-butanediyl) bis(oxy)] bis [N, N, N-trimethyl]-, dichloride dihydrate

Molecular Formula/Molecular Weight: $C_{14}H_{30}C_{12}N_2O_4 \cdot 2H_2O$/ 397.34

Structure or Biochemical Description:

Structural Formula



Pharmacologic Class: Ester local anesthetic (Established Pharmacological Class)

2.2 Relevant INDs, NDAs, BLAs and DMFs

App type/#	Product	Sponsor/Applicant	Indication/Comment
NDA 008845	Quelicin (succinylcholine)	Hospira	Adjunct to general anesthesia, to facilitate tracheal intubation, and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

2.3 Drug Formulation

The product, Succinylcholine Chloride Injection, USP, Preservative-Free, is packaged in one configuration as a 5 mL fill (20 mg/mL concentration) in a 5 mL single dose prefilled syringe.

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 (b) (4)	pH adjuster	To adjust pH to 3.0 to 4.5			ADJ PH
(b) (4)					

Container/Closure System 5 mL PFS		
Container/Closure Item	**Hikma Part Number**	**Description**
Barrel Syringe	(b) (4)	
Plunger Stopper		
Plunger Rod		

2.4 Comments on Novel Excipients

No novel excipients are used. Sodium chloride ((b) (4) hydrochloric acid (b) (4) (as a pH adjustors); and (b) (4) are the excipients used in the drug product.

2.5 Comments on Impurities/Degradants of Concern

The maximum recommended dose of this drug product is 600 mg/day, which will be used to establish the qualification thresholds for drug substance and drug product specifications.

Drug Substance (DS)

The impurities identified and characterized in the drug substance are the following (also see Table below):

a) Succinic acid
b) Succinylmonocholine chloride
c) (b) (4)
d) Unidentified Impurity 1 and 2

Listing of Potential Impurities	
IUPAC Chemical Name	(b) (4)
Succinic Acid	
Unidentified impurity 1 and 2 (b) (4)	
(b) (4)	
(b) (4) Succinylmonocholine Chloride)	
(b) (4)	

*Specified unidentified impurities from the USP drug substance monograph.

The following table summarizes the Applicant's proposed specifications for impurities and residual solvents in the drug substance:

Specified Identified Impurities							
Chemical Name	Code #	MDD	QT (%)	QT (TDI)	Regulatory QT Threshold (%)	Proposed AC (%)	Justification if proposed AC (%) > Regulatory QT Threshold (%)
Succinic Acid	(b) (4)	600 mg/day	(b) (4)			NMT 0.1%	The proposed acceptance criterion is aligned with the limit in the current USP drug substance monograph (0.1%).
(b) (4) (Succinylmonocholine Chloride) (b) (4)						NMT 0.4%	The impurity is a significant metabolite of the drug substance and the proposed acceptance criterion is aligned with the limit in the current USP drug substance monograph (0.4%). (b) (4)

Specified Unidentified Impurities							
Relative Retention Time	Code #	MDD	IT (%)	IT (TDI)	Regulatory IT Threshold (%)	Proposed AC (%)	Justification if proposed AC (%) > Regulatory IT Threshold (%)
(b) (4) Unidentified impurity 1 and 2 (b) (4)	N/A	600 mg/day	(b) (4)			NMT 0.4%	The proposed acceptance criterion is aligned with the limit in the current USP drug substance monograph (0.4%).

Unspecified Impurities					
MDD	IT (%)	IT (TDI)	Regulatory IT Threshold (%)	Proposed AC (%)	Not acceptable if proposed AC (%) > Regulatory IT Threshold (%)
600 mg/day	(b) (4)				

Total Impurities		
Total Impurities	Proposed AC (%)	Justification
(b) (4)	NMT 1.5%	Limit aligns with the limit in the current USP monograph.

The proposed specification for Residual Solvents in Succinylcholine Chloride, USP drug substance is: (b) (4): NMT (b) (4) ppm.

The proposed specifications for all the drug substance impurities (i.e., succinylmonocholine chloride, unidentified Impurity 1 and Impurity 2, as shown in the

Tables above) are above the appropriate identification and qualification thresholds of NMT (b) (4) per the ICH Q3A(R2) guidance for industry Q3A(R2) Impurities in Drug Substances. However, it can be noted that the above specifications for the drug substance impurities are within the maximum limit for these impurities for the drug substance in the referenced product. Furthermore, it can be pointed out that in humans, nearly all administered succinylcholine (SC) is rapidly hydrolyzed (within minutes) by butyrylcholinesterase in the liver and plasma to succinylmonocholine (SMC), which is a known major human metabolite of SC. Therefore, the levels of SMC produced as an impurity and DP degradant are qualified by safety information for the metabolite in nonclinical and clinical studies. (b) (4) (b) (4) (b) (4) Therefore, potential exposure to SMC and both succinic acid (b) (4) based on the proposed specifications and the MRHD of succinylcholine do not pose any further risk for patient safety. The drug substance specifications are acceptable based on the referenced product specification.

The specification limits for the residual solvents are acceptable as they are within permissible daily exposure (PDE) levels in accordance with the ICH guideline for industry Q3C Residual Solvents.

Drug Product (DP)

The proposed release and shelf-life specifications for Succinylcholine Chloride Injection drug product degradants are described in the following tables (Applicant's Table 4 to Table 7). However, the CMC reviewer observed that the highest level of succinylmono-choline chloride, (b) (4) and total degradation for the 15-month long-term stability studies is (b) (4) %, (b) (4) and (b) (4) %, respectively, which did not support the proposed acceptance criteria. Therefore, the CMC review team asked the Applicant to tighten the acceptance criteria based on the stability data. Accordingly, the Applicant proposed new acceptance criteria for succinylmono-choline chloride, (b) (4) (b) (4) and total degradation products as described in Table 1 below.

Table 4: Specified Identified Degradation Products

Chemical Name	Code #	MDD[K]	QT[L] (%)	QT[M] (TDI)	Regulatory QT Threshold (%)	Proposed AC[N] (%)	Justification if proposed AC (%) > Regulatory QT Threshold (%)
Succinic Acid	(b) (4)	600 mg/day	(b) (4)			(b) (4	(b) (4)
Succinylmono-choline Chloride							

Table 5: Specified Unidentified Degradation Products

Relative Retention Time	Code #	MDD	IT[O] (%)	IT (TDI)	Regulatory IT Threshold[P] (%)	Proposed AC (%)	Justification if proposed AC (%) > Regulatory IT Threshold (%)
(b) (4) Unidentified impurity 1 and 2 (b) (4)	N/A	600 mg/day	(b) (4)			Release: NMT 0.4% Shelf Life: NMT 0.4%	The observed level and the proposed AC for the impurity are adequately justified by the scientific literature. (USP Drug Substance Monograph)

Table 6: Unspecified Degradation Products

MDD	IT (%)	IT (TDI)	Regulatory IT Threshold (%)	Proposed AC (%)	Not acceptable if proposed AC (%) > Regulatory IT Threshold (%)
600 mg/day					(b) (4)

[K] MDD: Maximum Daily Dose of the drug product, in mg/day. The MDD value for Succinylcholine Chloride Injection USP (20 mg/mL) has been determined by the FDA to be 600 mg and is documented in a Discipline Review Letter dated 20Feb2020.
[L] QT: Qualification Threshold
[M] TDI: Total Daily Intake, in mg as per ICH Q3B QT value
[N] AC: Acceptance Criteria
[O] IT: Identification Threshold, ICH Q3B(R2)
[P] Based on lower intake of impurity from IT (%) or IT (TDI). If IT (TDI) is lower, express as %.

Table 7: Total Degradation Products

	Proposed AC (%)	Justification
Total Impurities (b) (4)		(b) (4)

Table 1: Current and Proposed Specifications

Test	Previous Stability Specification	Proposed Stability Specification
Degradation Products		(b) (4)
Succinylmonocholine		
Total Degradant[1]		

[1]Total Degradants specification includes results from (b) (4)

Specified Identified Degradation Products						
Chemical Name	MDD	QT	QT (TDI)	Regulatory QT	Proposed AC (%) and Justification if proposed AC > Regulatory QT Threshold	Release Batch data, 15-month LT stability data and 4-month stability data of RLD
Succinic Acid (b) (4)	600 mg/day	(b) (4)			(b) (4)	(b) (4)
Succinylmono-choline Chloride (b) (4)						

Specified Unidentified Degradation Products						
Relative Retention Time	MDD	IT	IT (TDI)	Regulatory IT Threshold	Proposed AC (%)	Justification if proposed AC > Regulatory IT Threshold
(b) (4) Unidentified Impurity 1 and 2 (b) (4)	600 mg/day	(b) (4)			Release: NMT 0.4% Shelf Life: NMT 0.4% (b) (4) And current drug substance USP monograph: 0.4%.)	Current drug substance USP monograph: 0.4%. (b) (4)

Total Degradation Products	
Proposed AC (%)	Justification
(b) (4)	

Based on a maximum daily dose of 600 mg, the appropriate ICH Q3B(R2) qualification threshold is NMT (b) (4) or (b) (4) mg, whichever is lower. A specification of NMT (b) (4) would result in maximum potential exposure of (b) (4) mcg per day, therefore the appropriate qualification specification may be NMT (b) (4) mcg per day, to provide adequate qualification in accordance with ICH Q3B(R2). As shown in the table above, the proposed shelf-life specification for succinylmonocholine at NMT (b) (4), (b) (4) at NMT (b) (4), and unidentified Impurity 1 and 2 at NMT 0.4% exceed the ICH QT indicated above. However, as noted above (for Drug Substance impurities), the safety of these degradants are qualified by the safe history of systemic exposure to these compounds as major human metabolites, and/or the proposed specifications are within the limits of the referenced succinylcholine chloride injection product.

The proposed specifications for unidentified impurities and the residual solvent (b) (4) are within the ICH Q3B(R2) identification threshold and PDE as per ICH Q3C, respectively. Therefore, there are no concerns with respect to safety in humans for these impurities in the drug product from the nonclinical perspective.

Container Closure System

The proposed drug product, Succinylcholine Chloride Injection, USP, Preservative-Free, is packaged as a 5 mL fill (20 mg/mL concentration) in a 5 mL single dose prefilled syringe and sealed with an (b) (4) closure and a subsequent (b) (4) plunger rod. The components used in the container closure system for Succinylcholine Chloride Injection, USP, Preservative-Free, 20 mg/mL in 5 mL syringes manufactured at Hikma Pharmaceuticals, Cherry Hill, NJ, are summarized in the Applicant's Table 1 and Table 2 below.

Table 1: Summary of Container Closure System

Container/Closure Item	Hikma Part Number	Description
Syringe Barrel	(b) (4)	
Plunger Stopper		
Plunger Rod		
Flow Wrap		

Extractables and leachables studies were performed to qualify the safety of the container closure system for the proposed clinical use and shelf-life of 15 months at 2-8°C.

Extraction Studies

Hikma conducted two sets of extractable studies to generate a comprehensive extractable profile for the container closer system. One was a control extraction study on individual primary and secondary packaging components and the second one was an extractable study on an assembled PFS system. Both of the extraction studies were designed based on the recommendations provided in USP <1663> and the Product Quality Research Institute (PQRI) with respect to extraction solutions, stoichiometry, temperatures, and times. The primary and secondary components of the 5 mL syringe system and the extractable studies performed on each component are described in the table (Applicant's Table 2) below.

Table 2: Summary of Container Closure System and Extraction Conditions					
Component	Extraction Conditions			Analytical Instruments used for Analysis	Reference Section
	Solvents	Type of extractions	Surface Area to Volume		
(b) (4)					

Analytical Evaluation Threshold

The Applicant determined the analytical evaluation threshold (AET) for Succinylcholine Chloride Injection, USP based on the following properties of the drug product:

- Maximum daily dose (MDD) of the product = 600 mg.
- The product's concentration = 20 mg/mL.
- The product's maximum daily volume (MDV) at MDD = 30 mL or 6 x 5 mL syringes.
- Since Succinylcholine Chloride Injection is not a chronic use drug product (< 10 years total life time exposure), the Applicant used (b) (4) mcg/day as the Safety Concern Threshold (SCT) for the AET calculation, which is appropriate.
- An additional uncertainty factor of (b) (4) was also included.

- The AET is,

$$AET = \frac{\text{Safety Concern Threshold (SCT)}}{\text{Maximum Daily Volume (MDV)}} \times \text{Uncertenity Factor (UF)}$$

Using above equation,

(b) (4)

Based on the CMC reviewer, the extraction methods were considered adequate and the limit of quantitation (LOQ) of (b) (4) mcg/mL for organic leachables and PDE principles for USP <232> elemental impurities was below the AET for all detection methods in the extraction method protocol. Numerous potential leachables including elemental impurities were identified in the extraction study and these potential leachables were then assessed in the Leachable Study.

Leachables Study

To evaluate the presence of leachables, extractables detected above the (b) (4) mcg/day SCT in the extraction studies of individual components and assembled PFS extractable study were considered as targets for demonstrating the method feasibility for Succinylcholine Chloride Injection leachable screening. Also, the extractable studies on individual components were matched with the extractables detected from the simulated study on assembled PFS. The table below (Applicant's Table 16) summarizes the leachable target selection.

Table 16: The Leachable Targets for Succinylcholine Chloride Injection

Detected Extractables*	Reason for Extractables Selecting as Target for leachable screen	Targets for Leachable Screen
(b) (4)		

Table 16: The Leachable Targets for Succinylcholine Chloride Injection

(b) (4)

Leachable Testing Results

Based on the review of the CMC reviewer, the leachable screening methods are acceptable for LOQ, specificity, and recovery using target leachables. The LOQ and spike recoveries of various target molecules were at (b) (4) mcg/mL, which is (b) (4) of the AET of (b) (4) mcg/mL.

Leachable screening was conducted with 3 lots of stability samples. Since, the Succinylcholine Chloride Injection is a refrigerated product (2-8ºC) with a proposed shelf life of at least 15 months, to understand the leaching kinetics to assess the safety of the product, 0-month (bulk solution without contact with CCS), 12-month, and 18-month long-term stability samples were screened for leachables. Leachable screening results are listed in Applicant's Table 17 (below).

(b) (4)

(b) (4)

Toxicological Risk Assessments

(b) (4)

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(b) (4)

2.6 Proposed Clinical Population and Dosing Regimen

- Recommended dose in adults (2.1)
  - For short surgical procedures: 0.6 mg/kg injection given intravenously
  - For long surgical procedures: 2.5 and 4.3 mg per minute
- Recommended dose in pediatrics (2.2)
  - For tracheal intubation in infants: 2 mg/kg
  - For tracheal intubation in older pediatric patients, and adolescents: 1 mg/kg

2.7 Regulatory Background

3 Studies Submitted and Reviewed

Leachable Assessment of Product Contact Parts for Succinylcholine Chloride Injection, USP, 20 mg/mL; 5 mL Fill in a 5 mL Syringe

3.3 Previous Reviews Referenced

None

4 Pharmacology

No new pharmacology studies were submitted with this NDA or required for this 505(b)(2) application. According to the referenced product labeling:

Succinylcholine is a depolarizing skeletal muscle relaxant. As does acetylcholine, it combines with the cholinergic receptors of the motor end plate to produce depolarization. This depolarization may be observed as fasciculations. Subsequent neuromuscular transmission is inhibited so long as adequate concentration of succinylcholine remains at the receptor site. Onset of flaccid paralysis is rapid (less than one minute after intravenous administration), and with single administration lasts approximately 4 to 6 minutes.

The paralysis following administration of succinylcholine is progressive, with differing sensitivities of different muscles. This initially involves consecutively the levator muscles of the face, muscles of the glottis and finally the intercostals and the diaphragm and all other skeletal muscles.

5 Pharmacokinetics/ADME/Toxicokinetics

No new nonclinical PK/ADME/TK studies were submitted with this NDA or required for this 505(b)(2) application.

6 General Toxicology

No new nonclinical general toxicology studies were submitted with this NDA or required for this 505(b)(2) application as an adequate bridge (i.e., biobridge) was established for this product to the referenced product Quelicin.

7 Genetic Toxicology

No new genetic toxicology studies were conducted for this NDA or required for this 505(b)(2) application. The Applicant is relying upon the Agency's previous finding of safety for Quelicin. The referenced product label does not include nonclinical genetic toxicology data and currently states the following:

Genetic toxicology studies have not been completed to evaluate the genotoxic potential of succinylcholine.

8 Carcinogenicity

No carcinogenicity studies were submitted with the NDA and none were required as the proposed use is for an acute indication. The Applicant is relying upon the Agency's previous finding of safety for Quelicin. The referenced product label does not include any carcinogenicity data.

9 Reproductive and Developmental Toxicology

No new nonclinical reproductive and developmental toxicology studies were submitted with this NDA or required for this 505(b)(2) application. The Applicant is relying upon the Agency's previous finding of safety for Quelicin. The referenced product label does not include any nonclinical reproductive and developmental toxicity data.

As part of the requirement under the Pregnancy Lactation and Labeling Rule (PLLR), the Applicant was required to conduct a review of the literature to determine if there are any reproductive and developmental toxicity data for succinylcholine chloride in the public domain. However, during preliminary review it was found that the Applicant did not provide a full list of the nonclinical articles that were identified related to the potential developmental and reproductive toxicity of succinylcholine or their rationale for including or not including specific findings in the label in their submission. Therefore, an Information Request was sent asking the Applicant to submit all relevant articles to the NDA and provide a summary for each article that includes a justification for why the findings should or should not be included in labeling.

In their response (SDN 6, 01/14/2021), the Applicant provided a report documenting the systematic literature search strategy, and results of their search which identified 3 articles with respect to relevant nonclinical studies identified in the search activity. Based on the narrative of their search strategy it appears that their primary search activity focused on PUBMED and other databases using the appropriate keywords covering the period from 1950 to June 2020. As stated above, the Applicant identified three (3) publications that they proposed to have relevant information based on their validity criteria.

This Reviewer also conducted an independent search and identified two articles that were related to reproductive or developmental toxicities of succinylcholine in animals. Upon preliminary review of the studies listed in the search activity, the reviewer determined that the study by Drabkova et al. (1973) was identified both by the Applicant and the reviewer. However, the other two studies (Gibbs 1974, and Moya and Kvisselgard 1961) were not relevant as the one by Gibbs et al. was a review article (not original article) and the other was a clinical study where unpublished nonclinical studies

examining the effect of succinylcholine in full term rabbits were reported. All three articles identified by the Applicant are listed below.

1. Drábková J, Crul JF, van der Kleijn E. Placental transfer of 14C labelled succinylcholine in near-term Macaca mulatta monkeys. Br J Anaesth. 1973;45(11):1087-96.

2. Gibb DB. Suxamethonium--a review. Pharmacological actions of suxamethonium apart from its neuromuscular blocking effect. Anaesth Intensive Care. 1974;2(1):9-26.

3. Moya F, Kvisselgaard N. The placental transmission of succinylcholine. Anesthesiology. 1961;22:1-6.

This reviewer evaluated the original articles by Drabkova et al. (1973) (identified both by the Applicant and the reviewer) and Wiqvist and Wahlin (1962) and summary of the evaluations of these studies are described below.

1. Drabkova, J. Crul, J. F. and Van der Kleijn, E. Placental transfer of ^{14}C-labeled succinylcholine in near term Macaca mulatta monkeys. Br J Anaesth. 1973;45(11):1087-96.

The data showing transfer of succinylcholine (SC) across the placental barrier has been controversial. There are studies that suggest there is no transfer across placental membrane after injection of SC in the mother. However, in animal studies, a rapid placental transmission of similar drugs like hexamethonium and decamethonium, has been observed with their ^{14}C radiolabel analogs in rats and rabbits. Pseudo cholinesterase that breaks SC to inactive metabolites is found to be lower in plasma of pregnant women and also in the newborn infants. Thus, the authors of this study argue that there is a distinct possibility that SC could transfer across placental barrier and then could have untoward effects on the fetus. Accordingly, these authors undertook the study with ^{14}C labelled SC to evaluate if there is transfer of SC across placental membrane in *Macaca mulatta* (Rhesus) monkeys.

Twenty-three near-term *Macaca mulatta* monkeys (weight range 3.5-11.0 kg) were studied. The age of gestation was determined by the progress of ossification in the fetus. A femoral artery and a vein were cannulated. After laparotomy the uterus was exposed. One of the interplacental branches of the umbilical vein coming from the succenturiate placenta was dissected and cannulated against the direction of blood flow, keeping the amniotic sac intact. During the actual experiment the uterus lay in the abdominal cavity in its natural position. ^{14}C succinylcholine (NEN Corporation, specific activity 5 mcCi/mg/10 mL) was injected intravenously at a dose of 2 mL/kg. Sample size for determination of radioactivity were 1 mL for maternal blood, 0.1 mL for fetal blood and amniotic fluid. Samples (1 mL for maternal blood and 0.1 mL for fetal blood and amniotic fluid) were taken from the maternal femoral artery, the umbilical vein and from the amniotic sac.

Upon injection of ^{14}C succinylcholine intravenously, via the abdominal aorta or into the amniotic fluid, the radiolabel was found in fetal blood within 1 minute and showing peak between 5 to 10 min (see Table III and Fig 2 below). Moreover, the concentration ratio of fetal to maternal of ^{14}C succinylcholine was independent of the corresponding maternal concentration.

TABLE III. *Maternal and foetal plasma percentage concentrations of succinyldicholine, succinylmonocholine and choline at intervals after intravenous succinyldicholine (2 ml/kg body weight) injection to the mother (0=not measurable; —=not measured).*

Time (min)	Maternal plasma			Foetal plasma		
	Succinyldicholine (%)	Succinylmonocholine (%)	Choline (%)	Succinyldicholine (%)	Succinylmonocholine (%)	Choline (%)
1	29.6	70.4	0	—	—	—
2	22.2	87.8	0	—	—	—
3	—	—	—	52.2	47.8	0
5	12.4	87.6	0	34.1	65.9	0
10	3.5	88.7	7.8	18.5	81.5	0
15	1.3	93.6	5.1	16.7	83.3	0
20	0	97.1	2.9	—	—	—

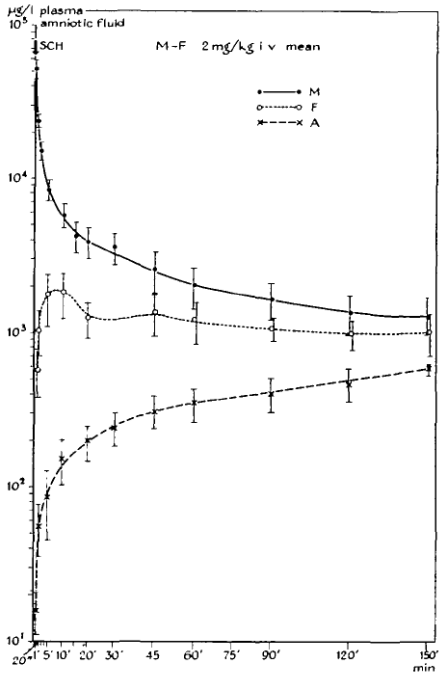


FIG. 2. Concentration time course of radioactivity in maternal plasma (M), foetal plasma (F) and amniotic fluid (A) after the administration of 2 mg succinylcholine/kg body weight intravenously to the mother. Means and standard deviations of the means for 5 experiments.

However, following intra-aortic injection peak fetal concentrations were reached earlier and were approximately 3 times higher than after the same dose given intravenously (Fig 6).

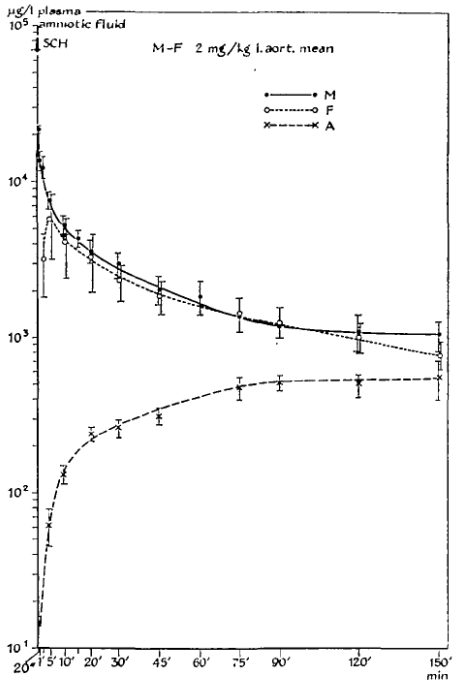


FIG. 6. Concentration time course of radioactivity in maternal plasma (M), foetal plasma (F) and amniotic fluid (A) after the administration of 2 mg succinylcholine/kg body weight into the abdominal aorta of the mother. Means and standard deviations of the means for 3 experiments.

Intravenous injection of 3 mg/kg of ^{14}C succinylcholine in the mother lead to concentration time course in the maternal plasma that was significantly different from that from 2 mg/kg dose; however, the time to reach the peak effects and peak concentration in fetal circulation were similar (Figs 2 and 5). Furthermore, repeated intravenous dosing in the mother lead to concentration of ^{14}C succinylcholine in the amniotic fluid that was additive. Based on their data the authors concluded that although smaller doses of 1 mg/kg of succinylcholine in obstetric anesthesia before delivery may not endanger the fetus, larger doses or small doses at repeated dose intervals may affect the neuromuscular transmission in the fetus and newborn.

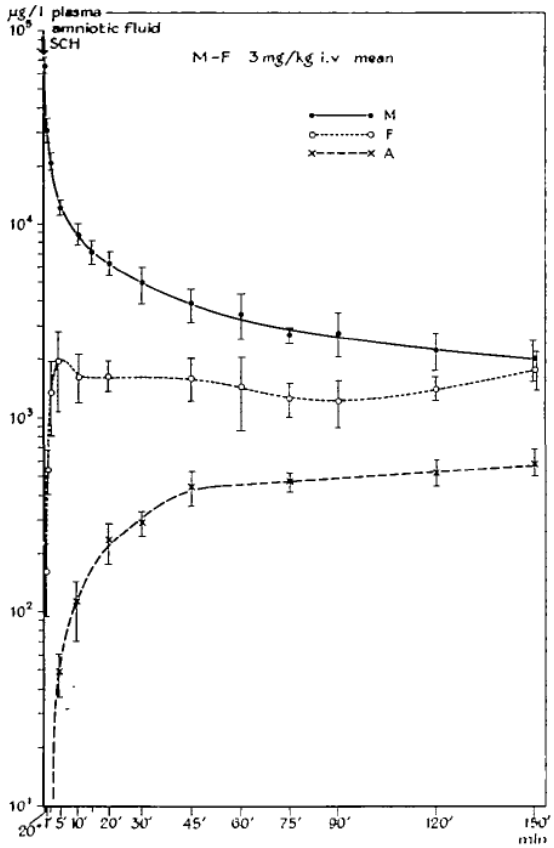


FIG. 5. Concentration time course of radioactivity in maternal plasma (M), foetal plasma (F) and amniotic fluid (A) after the administration of 3 mg succinylcholine/kg body weight intravenously to the mother. Means and standard deviations of the means for 4 experiments.

Reviewer's Note: There have been conflicting reports on the transfer of succinylcholine across placental barrier in rhesus monkeys. Using ^{14}C succinylcholine, a radiolabeled succinylcholine analog, the authors of this study demonstrated quite convincingly that there is transfer of SC across placental membrane from the mother to the fetus and that such transfer could lead to altered neuromuscular transmission in the fetus and newborn. However, this observation was discussed with the clinical and maternal health (MH) team to determine if such information would be useful to the clinician for prescribing the product given that the proposed labeling includes human data describing placental transmission of succinylcholine. Therefore, even though the reviewer concurs with the Applicant stance that such information is important, at this point I am not convinced that the information need be included in the PI given the human data.

2. Wiqvist N, Wahlin A. Effect of succinylcholine on uterine motility. Acta Anaesthesiol Scand. 1962;6:71-5

Vertebrate non-striated muscles are categorized into two types: multi-unit muscles/striated and visceral or smooth muscles. The former group includes the nictitating membrane and the muscles in the blood-vessel walls and their conduction is mediated by autonomic nerve fibers. Succinylcholine induces relaxation of these muscles. On the other hand, in smooth muscle organs represented by intestine, ureter

and uterus, conduction is propagated from muscle fiber to fiber. The authors states that very few studies have been made on the effect of succinylcholine on this group (during the time the study has been published). In the published study, the authors wanted to study whether succinylcholine had any influence on the uterine motility and tone in animals and on human subjects.

Spontaneous uterine motility was recorded in vivo in the non-pregnant cat and rat. Anesthetized animals were maintained on a ventilator. The uterus was cannulated with a polythene tube after incision through the midline. The polythene tube was connected with a transducer and the intra-uterine pressure recorded on a Grass instrument. Carotid arteries were cannulated to measure arterial pressure. In humans, pregnant women at the third or fourth month of gestation undergoing legal abortion were included. The amniotic cavity was punctured transabdominally with a needle; a thin polythene catheter was introduced, and the amniotic pressure recorded. In cats, 1-2 mg of succinylcholine in 1 mL Ringer solution did not change the uterine motility. In rats, even a higher dose of 3 mg that was sufficient to cause respiratory arrest did not result in noticeable change in uterine contractility or rhythm (Fig 1).

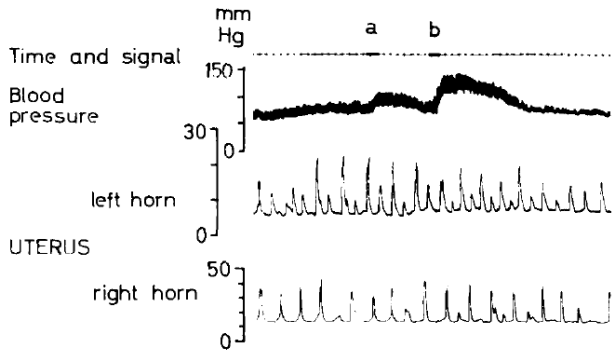


Fig. 1.—Effect of succinylcholine on uterine motility and blood pressure of the non-pregnant rat. Intra-uterine pressure recorded from both horns. Time marking: 30 sec.
a) Intravenous injection of 0.3 ml Ringer solution.
b) Intravenous injection of 3 mg succinylcholine in 0.3 ml Ringer solution.

The authors also concluded that succinylcholine did not have any effect on the human uterus as it did not block the appearance of strong uterine contractions induced by oxytocin.

Reviewer's note: This study was conducted in 1962, which is more than 50 years ago. The setup of the experimental techniques as well as results are pretty straight forward. However, it is not clear to this reviewer how many rats and cats each were used in the study. Moreover, the study lacks some details, e.g., no positive controls were used in the experiment. Therefore, even though the results are intriguing, this reviewer does not find it necessary to include the information in the label. Given the extensive clinical use of the drug, data from humans is more appropriate to inform any labeling recommendations.

10 Special Toxicology Studies

No special toxicology studies were submitted with this NDA.

11 Integrated Summary and Safety Evaluation

NDA 215143 was submitted to seek marketing approval for Succinylcholine Chloride Injection, USP 20 mg/mL, as an adjunct to general anesthesia, to facilitate tracheal intubation, and to provide skeletal muscle relaxation during surgery or mechanical ventilation. The NDA was submitted as a 505(b)(2) application relying on the Agency's previous finding of safety and efficacy of the listed drug QUELICIN™ (succinylcholine chloride injection, USP) approved under NDA 008845 for Hospira, Inc. Since the NDA is a 505(b)(2) application and an adequate scientific bridge was established between this product and the referenced product indicating that exposures are comparable, no new nonclinical studies for succinylcholine were submitted with this NDA or required.

Drug substance impurities and drug product degradants are either within specification limits according to ICH Q3A(R2) and Q3B(R2) guidances, respectively, or their levels can be justified to be safe for human use based on prevailing data for the referenced approved product for the same route and indication. In addition, the detected degradants succinylmonocholine and succinic acid are major human metabolites, and therefore, the specifications are considered adequate.

Although numerous potential leachables including elemental impurities were identified during the extractable study with the container closure system, only 2 organic and 2 USP <232> elemental leachables were found in the long-term stability sample at or above the default reporting limit of (b) (4) mcg/mL. Nevertheless, the maximum levels of these organic compounds and elemental impurities that could be potentially administered daily to humans are not of human safety concern as they are within the permissible daily exposure limits for these organic compounds and elemental impurities.

12 Appendix/Attachments

N/A

References

A. Drabkova, J. Crul, J. F. and Van der Kleijn, E. Placental transfer of 14C-labeled succinylcholine in near term Macaca mulatta monkeys. Br J Anaesth. 1973;45(11):1087-96.
B. Wiqvist N, Wahlin A. Effect of succinylcholine on uterine motility. Acta Anaesthesiol Scand. 1962;6:71-5.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

IMRAN M KHAN
08/20/2021 11:39:53 AM

RICHARD D MELLON on behalf of JAY H CHANG
08/20/2021 12:07:08 PM

RICHARD D MELLON
08/20/2021 12:08:40 PM
I concur. This document replaces the previously submitted review to correct an inaccuracy.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	215143
Supporting document/s:	SDN 1, 10/01/2020; SDN 6, 01/14/2021
Applicant's letter date:	October 01, 2020
CDER stamp date:	October 01, 2020
Product:	Succinylcholine Chloride Injection, USP, Preservative-Free; 100 mg/5 mL (20 mg/mL) Pre-Filled Syringes
Indication:	As an adjunct to general anesthesia, to facilitate tracheal intubation, and to provide skeletal muscle relaxation during surgery or mechanical ventilation
Applicant:	Hikma Pharmaceuticals USA Inc.
Clinical Review Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Reviewer:	Imran M. Khan, PhD
Supervisor:	Jay H. Chang, PhD
Deputy Director:	R. Daniel Mellon, PhD
Clinical Division Director:	Rigoberto Roca, MD
Project Manager:	Sandy Truong, PharmD

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 215143 are owned by Hikma Pharmaceuticals USA Inc. or are data for which Hikma Pharmaceuticals USA Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 215143 that Hikma Pharmaceuticals USA Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 215143.

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

NDA 215143 was submitted to seek marketing approval for Succinylcholine Chloride Injection, USP 20 mg/mL, as an adjunct to general anesthesia, to facilitate tracheal intubation, and to provide skeletal muscle relaxation during surgery or mechanical ventilation. The NDA was submitted as a 505(b)(2) application relying on the Agency's previous finding of safety and efficacy of the listed drug QUELICIN™ (succinylcholine chloride injection, USP) approved under NDA 008845 for Hospira, Inc. The approved products under the referenced NDA, QUELICIN is indicated for the same indication as described above.

1.2 Brief Discussion of Nonclinical Findings

No new nonclinical toxicological studies were submitted with the NDA.
Drug substance impurities and drug product degradants are either within specification limits according to the ICH Q3A(R2) and Q3B(R2) guidances, respectively, or their levels can be justified to be safe for human use based on the levels being within the approved referenced product.

Extractables and leachables studies were performed to justify the safety of the proposed container closure system, which consists of a 5 mL prefilled plastic syringe with plastic tip cap, plunger stopper, plunger rod, and adhesive label. Although numerous potential leachables including elemental impurities were identified in the extractables study with the container closure system, only two organic compounds (b) (4) (b) (4) and 2 USP <232> elemental leachables (b) (4)) were found in the long-term stability sample at or above the Applicant's reporting limit of (b) (4) mcg/mL. The levels of (b) (4) are not of human safety concern as the permissible daily exposure (PDE) levels for these leachables are higher than the maximum daily intake (MDI) that patients could be exposed to via administration of the drug product at the maximum recommended daily dose. Although there are no toxicological data for (b) (4) to determine the PDE for this leachable, QSAR analysis both by the Applicant and the Agency find it to be non-mutagenic. Moreover, analysis of the toxicological data available for appropriate surrogate compounds for (b) (4) provide PDEs that indicate that MDI of (b) (4) mg/day for the leachable impurity does not present a safety concern for humans with the parenteral administration of the drug product. Therefore, we have no safety concern regarding potential leachables arising from the container closure system.

In addition, the Applicant provided (b) (4)
(b) (4)

(b) (4)

1.3 Recommendations

1.3.1 Approvability

From a nonclinical perspective, the NDA may be approved. However, the proposed labeling might require further discussion among the nonclinical, clinical, and maternal health review teams before a final labeling revision is recommended.

1.3.2 Additional Non Clinical Recommendations

N/A

1.3.3 Labeling

The Applicant's proposed label language is shown in the 2nd column (from left) of the table below. The right columns summarize this reviewer's recommended changes, rationale for this reviewer's recommended changes and general comments. The final label, which will be based on further internal discussion and negotiations with the Applicant, can be found in the Action letter.

Listed Drug (QUELICIN) Labeling	Applicant's Proposed Labeling	Recommended Changes to Proposed Labeling	Rationale for recommended changes/Comment
(b) (4)			

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

There are no studies to evaluate the potential impact of succinylcholine on fertility.	There are no studies to evaluate the potential impact of succinylcholine on fertility.	Impairment of Fertility There are no studies to evaluate the potential impact of succinylcholine on fertility.	

2 Drug Information

2.1 Drug

CAS Registry Number: 6101-15-1

Generic Name: Succinylcholine Chloride

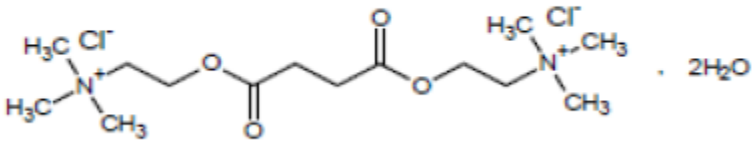
Code Name: N/A

Chemical Name: Ethanaminium, 2,2'-[(1,4-dioxo-1,4-butanediyl) bis(oxy)] bis [N, N, N-trimethyl]-, dichloride dihydrate

Molecular Formula/Molecular Weight: $C_{14}H_{30}C_{12}N_2O_4 \cdot 2H_2O$/ 397.34

Structure or Biochemical Description:

Structural Formula



Pharmacologic Class: Ester local anesthetic (Established Pharmacological Class)

2.2 Relevant INDs, NDAs, BLAs and DMFs

App type/#	Product	Sponsor/Applicant	Indication/Comment
NDA 008845	Quelicin (succinylcholine)	Hospira	Adjunct to general anesthesia, to facilitate tracheal intubation, and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

2.3 Drug Formulation

The product, Succinylcholine Chloride Injection, USP, Preservative-Free, is

packaged in one configuration as a 5 mL fill (20 mg/mL concentration) in a 5 mL single dose prefilled syringe.

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	pH adjuster	To adjust pH to 3.0 to 4.5			ADJ PH
(b) (4)					(b) (4)

Container/Closure System 5 mL PFS		
Container/Closure Item	**Hikma Part Number**	**Description**
Barrel Syringe	(b) (4)	
Plunger Stopper		
Plunger Rod		

2.4 Comments on Novel Excipients

No novel excipients are used. Sodium chloride (b) (4), hydrochloric acid (b) (4) (as a pH adjustors); and (b) (4) are the excipients used in the drug product.

2.5 Comments on Impurities/Degradants of Concern

The maximum recommended dose of this drug product is 600 mg/day, which will be used to establish the qualification thresholds for drug substance and drug product specifications.

Drug Substance (DS)

The impurities identified and characterized in the drug substance are the following (also see Table below):

a) Succinic acid
b) Succinylmonocholine chloride
c) (b) (4)
d) Unidentified Impurity 1 and 2

Listing of Potential Impurities	
IUPAC Chemical Name	(b) (4)
Succinic Acid	
Unidentified impurity 1 and 2 (b) (4)	
(b) (4) (Succinylmonocholine Chloride)	
(b) (4)	

*Specified unidentified impurities from the USP drug substance monograph.

The following table summarizes the Applicant's proposed specifications for impurities and residual solvents in the drug substance:

Specified Identified Impurities							
Chemical Name	Code #	MDD	QT (%)	QT (TDI)	Regulatory QT Threshold (%)	Proposed AC (%)	Justification if proposed AC (%) > Regulatory QT Threshold (%)
Succinic Acid	(b) (4)	600 mg/day	(b) (4)			NMT 0.1%	The proposed acceptance criterion is aligned with the limit in the current USP drug substance monograph (0.1%).
(b) (4) (Succinylmonocholine Chloride) (b) (4)						NMT 0.4%	The impurity is a significant metabolite of the drug substance and the proposed acceptance criterion is aligned with the limit in the current USP drug substance monograph (0.4%). (b) (4)

Specified Unidentified Impurities							
Relative Retention Time	Code #	MDD	IT (%)	IT (TDI)	Regulatory IT Threshold (%)	Proposed AC (%)	Justification if proposed AC (%) > Regulatory IT Threshold (%)
(b) (4) Unidentified impurity 1 and 2 (b) (4)	N/A	600 mg/day	(b) (4)			NMT 0.4%	The proposed acceptance criterion is aligned with the limit in the current USP drug substance monograph (0.4%).

Unspecified Impurities					
MDD	IT (%)	IT (TDI)	Regulatory IT Threshold (%)	Proposed AC (%)	Not acceptable if proposed AC (%) > Regulatory IT Threshold (%)
600 mg/day	(b) (4)				

Total Impurities		
Total Impurities (b) (4)	Proposed AC (%)	Justification
	NMT 1.5%	Limit aligns with the limit in the current USP monograph.

The proposed specification for Residual Solvents in Succinylcholine Chloride, USP drug substance is: (b) (4) : NMT (b) (4)

The proposed specifications for all the drug substance impurities (i.e., succinylmonocholine chloride, unidentified Impurity 1 and Impurity 2, as shown in the

Tables above) are above the appropriate identification and qualification thresholds of NMT (b) (4)% per the ICH Q3A(R2) guidance for industry Q3A(R2) Impurities in Drug Substances. However, it can be noted that the above specifications for the drug substance impurities are within the maximum limit for these impurities for the drug substance in the referenced product. Furthermore, it can be pointed out that in humans, nearly all administered succinylcholine (SC) is rapidly hydrolyzed (within minutes) by butyrylcholinesterase in the liver and plasma to succinylmonocholine (SMC), which is a known major human metabolite of SC. Therefore, the levels of SMC produced as an impurity and DP degradant are qualified by safety information for the metabolite in nonclinical and clinical studies. (b) (4)

(b) (4)

(b) (4) Therefore, potential exposure to SMC and both succinic acid (b) (4) based on the proposed specifications and the MRHD of succinylcholine do not pose any further risk for patient safety. The drug substance specifications are acceptable based on the referenced product specification.

The specification limits for the residual solvents are acceptable as they are within permissible daily exposure (PDE) levels in accordance with the ICH guideline for industry Q3C Residual Solvents.

Drug Product (DP)

The proposed release and shelf-life specifications for Succinylcholine Chloride Injection drug product degradants are described in the following tables (Applicant's Table 4 to Table 7). However, the CMC reviewer observed that the highest level of succinylmono-choline chloride, (b) (4) and total degradation for the 15-month long-term stability studies is (b) (4)%, (b) (4) and (b) (4)%, respectively, which did not support the proposed acceptance criteria. Therefore, the CMC review team asked the Applicant to tighten the acceptance criteria based on the stability data. Accordingly, the Applicant proposed new acceptance criteria for succinylmono-choline chloride, (b) (4) (b) (4) and total degradation products as described in Table 1 below.

Table 4: Specified Identified Degradation Products

Chemical Name	Code #	MDD[K]	QT[L] (%)	QT[M] (TDI)	Regulatory QT Threshold (%)	Proposed AC[N] (%)	Justification if proposed AC (%) > Regulatory QT Threshold (%)
Succinic Acid	(b) (4)	600 mg/day				(b) (4)	(b) (4)
Succinylmono-choline Chloride	(b) (4)						

Table 5: Specified Unidentified Degradation Products

Relative Retention Time	Code #	MDD	IT[O] (%)	IT (TDI)	Regulatory IT Threshold[P] (%)	Proposed AC (%)	Justification if proposed AC (%) > Regulatory IT Threshold (%)
(b) (4) Unidentified impurity 1 and 2 (b) (4)	N/A	600 mg/day	(b) (4)			Release: NMT 0.4% Shelf Life: NMT 0.4%	The observed level and the proposed AC for the impurity are adequately justified by the scientific literature. (USP Drug Substance Monograph)

Table 6: Unspecified Degradation Products

MDD	IT (%)	IT (TDI)	Regulatory IT Threshold (%)	Proposed AC (%)	Not acceptable if proposed AC (%) > Regulatory IT Threshold (%)
600 mg/day	(b) (4)				

[K] MDD: Maximum Daily Dose of the drug product, in mg/day. The MDD value for Succinylcholine Chloride Injection USP (20 mg/mL) has been determined by the FDA to be 600 mg and is documented in a Discipline Review Letter dated 20Feb2020.
[L] QT: Qualification Threshold
[M] TDI: Total Daily Intake, in mg as per ICH Q3B QT value
[N] AC: Acceptance Criteria
[O] IT: Identification Threshold, ICH Q3B(R2)
[P] Based on lower intake of impurity from IT (%) or IT (TDI). If IT (TDI) is lower, express as %.

Table 7: Total Degradation Products

	Proposed AC (%)	Justification
Total Impurities (b) (4)	(b) (4)	

Table 1: Current and Proposed Specifications

Test	Previous Stability Specification	Proposed Stability Specification
Degradation Products		(b) (4)
Succinylmonocholine	(b) (4)	
Total Degradant[1]		

[1] Total Degradants specification includes results from (b) (4)

Specified Identified Degradation Products						
Chemical Name	MDD	QT	QT (TDI)	Regulatory QT	Proposed AC (%) and Justification if proposed AC > Regulatory QT Threshold	Release Batch data, 15-month LT stability data and 4-month stability data of RLD
Succinic Acid (b) (4)	600 mg/day			(b) (4)	(b) (4)	(b) (4)
Succinylmono-choline Chloride (b) (4) (b) (4)						

Specified Unidentified Degradation Products						
Relative Retention Time	MDD	IT	IT (TDI)	Regulatory IT Threshold	Proposed AC (%)	Justification if proposed AC > Regulatory IT Threshold
(b) (4) Unidentified Impurity 1 and 2 (b) (4)	600 mg/day	(b) (4)			Release: NMT 0.4% Shelf Life: NMT 0.4% (b) (4) And current drug substance USP monograph: 0.4%.)	Current drug substance USP monograph: 0.4%. (b) (4)

Total Degradation Products	
Proposed AC (%)	Justification
	(b) (4)

Based on a maximum daily dose of 600 mg, the appropriate ICH Q3B(R2) qualification threshold is NMT (b) (4) or (b) (4) mg, whichever is lower. A specification of NMT (b) (4) would result in maximum potential exposure of (b) (4) mcg per day, therefore the appropriate qualification specification may be NMT (b) (4) mcg per day, to provide adequate qualification in accordance with ICH Q3B(R2). As shown in the table above, the proposed shelf-life specification for succinylmonocholine at NMT (b) (4) (b) (4) at NMT (b) (4), and unidentified Impurity 1 and 2 at NMT 0.4% exceed the ICH QT indicated above. However, as noted above (for Drug Substance impurities), the safety of these degradants are qualified by the safe history of systemic exposure to these compounds as major human metabolites, and/or the proposed specifications are within the limits of the referenced succinylcholine chloride injection product.

The proposed specifications for unidentified impurities and the residual solvent (b) (4) are within the ICH Q3B(R2) identification threshold and PDE as per ICH Q3C, respectively. Therefore, there are no concerns with respect to safety in humans for these impurities in the drug product from the nonclinical perspective.

Container Closure System

The proposed drug product, Succinylcholine Chloride Injection, USP, Preservative-Free, is packaged as a 5 mL fill (20 mg/mL concentration) in a 5 mL single dose prefilled syringe and sealed with an (b) (4) closure and a subsequent (b) (4) plunger rod. The components used in the container closure system for Succinylcholine Chloride Injection, USP, Preservative-Free, 20 mg/mL in 5 mL syringes manufactured at Hikma Pharmaceuticals, Cherry Hill, NJ, are summarized in the Applicant's Table 1 and Table 2 below.

Table 1: Summary of Container Closure System

Container/Closure Item	Hikma Part Number	Description
Syringe Barrel	(b) (4)	
Plunger Stopper		
Plunger Rod		
Flow Wrap		

Extractables and leachables studies were performed to qualify the safety of the container closure system for the proposed clinical use and shelf-life of 15 months at 2-8°C.

Extraction Studies

Hikma conducted two sets of extractable studies to generate a comprehensive extractable profile for the container closer system. One was a control extraction study on individual primary and secondary packaging components and the second one was an extractable study on an assembled PFS system. Both of the extraction studies were designed based on the recommendations provided in USP <1663> and the Product Quality Research Institute (PQRI) with respect to extraction solutions, stoichiometry, temperatures, and times. The primary and secondary components of the 5 mL syringe system and the extractable studies performed on each component are described in the table (Applicant's Table 2) below.

Table 2: Summary of Container Closure System and Extraction Conditions					
Component	Extraction Conditions			Analytical Instruments used for Analysis	Reference Section
	Solvents	Type of extractions	Surface Area to Volume		
(b) (4)					

Analytical Evaluation Threshold

The Applicant determined the analytical evaluation threshold (AET) for Succinylcholine Chloride Injection, USP based on the following properties of the drug product:

- Maximum daily dose (MDD) of the product = 600 mg.
- The product's concentration = 20 mg/mL.
- The product's maximum daily volume (MDV) at MDD = 30 mL or 6 x 5 mL syringes.
- Since Succinylcholine Chloride Injection is not a chronic use drug product (< 10 years total life time exposure), the Applicant used (b) (4) mcg/day as the Safety Concern Threshold (SCT) for the AET calculation, which is appropriate.
- An additional uncertainty factor of (b) (4) was also included.

- The AET is,

$$AET = \frac{\text{Safety Concern Threshold (SCT)}}{\text{Maximum Daily Volume (MDV)}} \times \text{Uncertenity Factor (UF)}$$

Using above equation,

(b) (4)

Based on the CMC reviewer, the extraction methods were considered adequate and the limit of quantitation (LOQ) of (b) (4) mcg/mL for organic leachables and PDE principles for USP <232> elemental impurities was below the AET for all detection methods in the extraction method protocol. Numerous potential leachables including elemental impurities were identified in the extraction study and these potential leachables were then assessed in the Leachable Study.

Leachables Study

To evaluate the presence of leachables, extractables detected above the (b) (4) mcg/day SCT in the extraction studies of individual components and assembled PFS extractable study were considered as targets for demonstrating the method feasibility for Succinylcholine Chloride Injection leachable screening. Also, the extractable studies on individual components were matched with the extractables detected from the simulated study on assembled PFS. The table below (Applicant's Table 16) summarizes the leachable target selection.

Table 16: The Leachable Targets for Succinylcholine Chloride Injection		
Detected Extractables*	**Reason for Extractables Selecting as Target for leachable screen**	**Targets for Leachable Screen**
(b) (4)		

Table 16: The Leachable Targets for Succinylcholine Chloride Injection

(b) (4)

Leachable Testing Results

Based on the review of the CMC reviewer, the leachable screening methods are acceptable for LOQ, specificity, and recovery using target leachables. The LOQ and spike recoveries of various target molecules were at (b) (4) mcg/mL, which is (b) (4) of the AET of (b) (4) mcg/mL.

Leachable screening was conducted with 3 lots of stability samples. Since, the Succinylcholine Chloride Injection is a refrigerated product (2-8ºC) with a proposed shelf life of at least 15 months, to understand the leaching kinetics to assess the safety of the product, 0-month (bulk solution without contact with CCS), 12-month, and 18-month long-term stability samples were screened for leachables. Leachable screening results are listed in Applicant's Table 17 (below).

(b) (4)

(b) (4)

Toxicological Risk Assessments

(b) (4)

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(b) (4)

2.6 Proposed Clinical Population and Dosing Regimen

- Recommended dose in adults (2.1)
  - For short surgical procedures: 0.6 mg/kg injection given intravenously
  - For long surgical procedures: 2.5 and 4.3 mg per minute
- Recommended dose in pediatrics (2.2)
  - For tracheal intubation in infants: 2 mg/kg
  - For tracheal intubation in older pediatric patients, and adolescents: 1 mg/kg

2.7 Regulatory Background

3 Studies Submitted and Reviewed

Leachable Assessment of Product Contact Parts for Succinylcholine Chloride Injection, USP, 20 mg/mL; 5 mL Fill in a 5 mL Syringe

3.3 Previous Reviews Referenced

None

4 Pharmacology

No new pharmacology studies were submitted with this NDA or required for this 505(b)(2) application. According to the referenced product labeling:

Succinylcholine is a depolarizing skeletal muscle relaxant. As does acetylcholine, it combines with the cholinergic receptors of the motor end plate to produce depolarization. This depolarization may be observed as fasciculations. Subsequent neuromuscular transmission is inhibited so long as adequate concentration of succinylcholine remains at the receptor site. Onset of flaccid paralysis is rapid (less than one minute after intravenous administration), and with single administration lasts approximately 4 to 6 minutes.

The paralysis following administration of succinylcholine is progressive, with differing sensitivities of different muscles. This initially involves consecutively the levator muscles of the face, muscles of the glottis and finally the intercostals and the diaphragm and all other skeletal muscles.

5 Pharmacokinetics/ADME/Toxicokinetics

No new nonclinical PK/ADME/TK studies were submitted with this NDA or required for this 505(b)(2) application.

6 General Toxicology

No new nonclinical general toxicology studies were submitted with this NDA or required for this 505(b)(2) application as an adequate bridge (i.e., biobridge) was established for this product to the referenced product Quelicin.

7 Genetic Toxicology

No new genetic toxicology studies were conducted for this NDA or required for this 505(b)(2) application. The Applicant is relying upon the Agency's previous finding of safety for Quelicin. The referenced product label does not include nonclinical genetic toxicology data and currently states the following:

Genetic toxicology studies have not been completed to evaluate the genotoxic potential of succinylcholine.

8 Carcinogenicity

No carcinogenicity studies were submitted with the NDA and none were required as the proposed use is for an acute indication. The Applicant is relying upon the Agency's previous finding of safety for Quelicin. The referenced product label does not include any carcinogenicity data.

9 Reproductive and Developmental Toxicology

No new nonclinical reproductive and developmental toxicology studies were submitted with this NDA or required for this 505(b)(2) application. The Applicant is relying upon the Agency's previous finding of safety for Quelicin. The referenced product label does not include any nonclinical reproductive and developmental toxicity data.

As part of the requirement under the Pregnancy Lactation and Labeling Rule (PLLR), the Applicant was required to conduct a review of the literature to determine if there are any reproductive and developmental toxicity data for succinylcholine chloride in the public domain. However, during preliminary review it was found that the Applicant did not provide a full list of the nonclinical articles that were identified related to the potential developmental and reproductive toxicity of succinylcholine or their rationale for including or not including specific findings in the label in their submission. Therefore, an Information Request was sent asking the Applicant to submit all relevant articles to the NDA and provide a summary for each article that includes a justification for why the findings should or should not be included in labeling.

In their response (SDN 6, 01/14/2021), the Applicant provided a report documenting the systematic literature search strategy, and results of their search which identified 3 articles with respect to relevant nonclinical studies identified in the search activity. Based on the narrative of their search strategy it appears that their primary search activity focused on PUBMED and other databases using the appropriate keywords covering the period from 1950 to June 2020. As stated above, the Applicant identified three (3) publications that they proposed to have relevant information based on their validity criteria.

This Reviewer also conducted an independent search and identified two articles that were related to reproductive or developmental toxicities of succinylcholine in animals. Upon preliminary review of the studies listed in the search activity, the reviewer determined that the study by Drabkova et al. (1973) was identified both by the Applicant and the reviewer. However, the other two studies (Gibbs 1974, and Moya and Kvisselgard 1961) were not relevant as the one by Gibbs et al. was a review article (not original article) and the other was a clinical study where unpublished nonclinical studies

examining the effect of succinylcholine in full term rabbits were reported. All three articles identified by the Applicant are listed below.

1. Drábková J, Crul JF, van der Kleijn E. Placental transfer of 14C labelled succinylcholine in near-term Macaca mulatta monkeys. Br J Anaesth. 1973;45(11):1087-96.

2. Gibb DB. Suxamethonium--a review. Pharmacological actions of suxamethonium apart from its neuromuscular blocking effect. Anaesth Intensive Care. 1974;2(1):9-26.

3. Moya F, Kvisselgaard N. The placental transmission of succinylcholine. Anesthesiology. 1961;22:1-6.

This reviewer evaluated the original articles by Drabkova et al. (1973) (identified both by the Applicant and the reviewer) and Wiqvist and Wahlin (1962) and summary of the evaluations of these studies are described below.

1. Drabkova, J. Crul, J. F. and Van der Kleijn, E. Placental transfer of ^{14}C-labeled succinylcholine in near term Macaca mulatta monkeys. Br J Anaesth. 1973;45(11):1087-96.

The data showing transfer of succinylcholine (SC) across the placental barrier has been controversial. There are studies that suggest there is no transfer across placental membrane after injection of SC in the mother. However, in animal studies, a rapid placental transmission of similar drugs like hexamethonium and decamethonium, has been observed with their ^{14}C radiolabel analogs in rats and rabbits. Pseudo cholinesterase that breaks SC to inactive metabolites is found to be lower in plasma of pregnant women and also in the newborn infants. Thus, the authors of this study argue that there is a distinct possibility that SC could transfer across placental barrier and then could have untoward effects on the fetus. Accordingly, these authors undertook the study with ^{14}C labelled SC to evaluate if there is transfer of SC across placental membrane in *Macaca mulatta* (Rhesus) monkeys.

Twenty-three near-term *Macaca mulatta* monkeys (weight range 3.5-11.0 kg) were studied. The age of gestation was determined by the progress of ossification in the fetus. A femoral artery and a vein were cannulated. After laparotomy the uterus was exposed. One of the interplacental branches of the umbilical vein coming from the succenturiate placenta was dissected and cannulated against the direction of blood flow, keeping the amniotic sac intact. During the actual experiment the uterus lay in the abdominal cavity in its natural position. ^{14}C succinylcholine (NEN Corporation, specific activity 5 mcCi/mg/10 mL) was injected intravenously at a dose of 2 mL/kg. Sample size for determination of radioactivity were 1 mL for maternal blood, 0.1 mL for fetal blood and amniotic fluid. Samples (1 mL for maternal blood and 0.1 mL for fetal blood and amniotic fluid) were taken from the maternal femoral artery, the umbilical vein and from the amniotic sac.

Upon injection of ^{14}C succinylcholine intravenously, via the abdominal aorta or into the amniotic fluid, the radiolabel was found in fetal blood within 1 minute and showing peak between 5 to 10 min (see Table III and Fig 2 below). Moreover, the concentration ratio of fetal to maternal of ^{14}C succinylcholine was independent of the corresponding maternal concentration.

TABLE III. *Maternal and foetal plasma percentage concentrations of succinyldicholine, succinylmonocholine and choline at intervals after intravenous succinyldicholine (2 ml/kg body weight) injection to the mother (0=not measurable; —=not measured).*

Time (min)	Maternal plasma			Foetal plasma		
	Succinyldicholine (%)	Succinylmonocholine (%)	Choline (%)	Succinyldicholine (%)	Succinylmonocholine (%)	Choline (%)
1	29.6	70.4	0	—	—	—
2	22.2	87.8	0	—	—	—
3	—	—	—	52.2	47.8	0
5	12.4	87.6	0	34.1	65.9	0
10	3.5	88.7	7.8	18.5	81.5	0
15	1.3	93.6	5.1	16.7	83.3	0
20	0	97.1	2.9	—	—	—

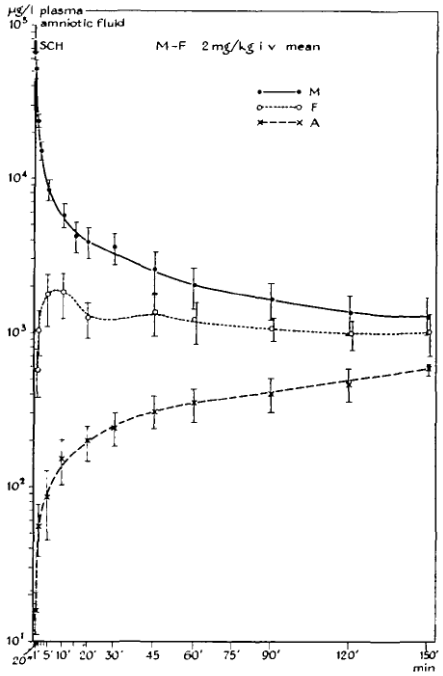

FIG. 2. Concentration time course of radioactivity in maternal plasma (M), foetal plasma (F) and amniotic fluid (A) after the administration of 2 mg succinylcholine/kg body weight intravenously to the mother. Means and standard deviations of the means for 5 experiments.

However, following intra-aortic injection peak fetal concentrations were reached earlier and were approximately 3 times higher than after the same dose given intravenously (Fig 6).

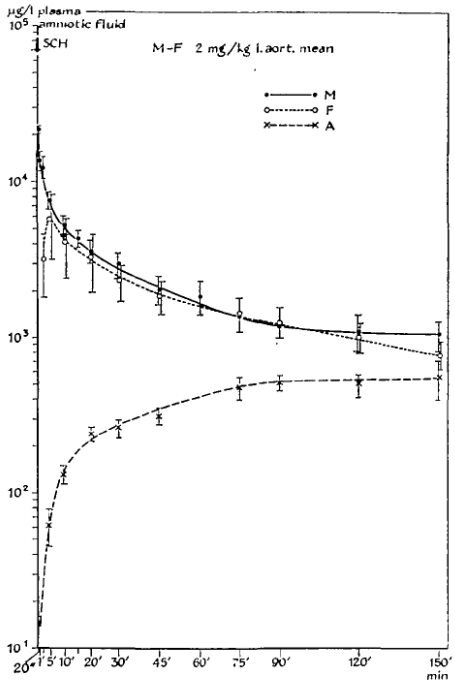

FIG. 6. Concentration time course of radioactivity in maternal plasma (M), foetal plasma (F) and amniotic fluid (A) after the administration of 2 mg succinylcholine/kg body weight into the abdominal aorta of the mother. Means and standard deviations of the means for 3 experiments.

Intravenous injection of 3 mg/kg of ^{14}C succinylcholine in the mother lead to concentration time course in the maternal plasma that was significantly different from that from 2 mg/kg dose; however, the time to reach the peak effects and peak concentration in fetal circulation were similar (Figs 2 and 5). Furthermore, repeated intravenous dosing in the mother lead to concentration of ^{14}C succinylcholine in the amniotic fluid that was additive. Based on their data the authors concluded that although smaller doses of 1 mg/kg of succinylcholine in obstetric anesthesia before delivery may not endanger the fetus, larger doses or small doses at repeated dose intervals may affect the neuromuscular transmission in the fetus and newborn.

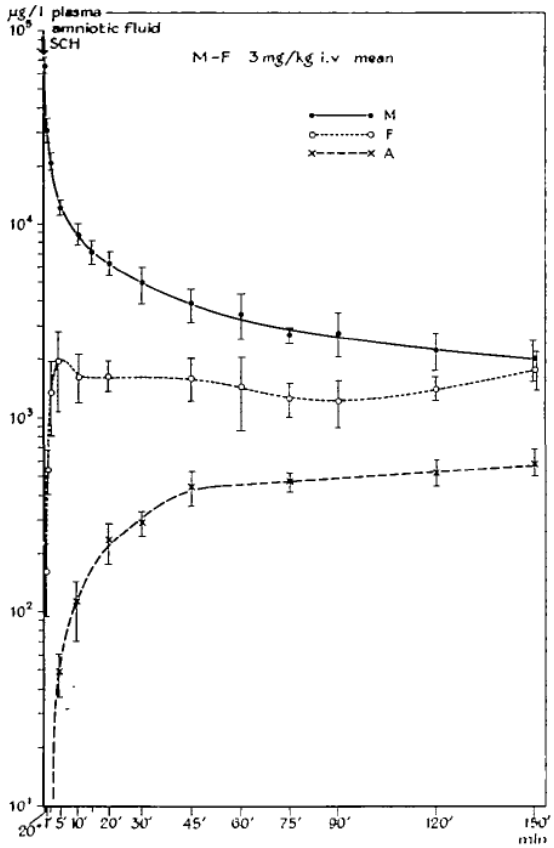

FIG. 5. Concentration time course of radioactivity in maternal plasma (M), foetal plasma (F) and amniotic fluid (A) after the administration of 3 mg succinylcholine/kg body weight intravenously to the mother. Means and standard deviations of the means for 4 experiments.

Reviewer's Note: There have been conflicting reports on the transfer of succinylcholine across placental barrier in rhesus monkeys. Using ^{14}C succinylcholine, a radiolabeled succinylcholine analog, the authors of this study demonstrated quite convincingly that there is transfer of SC across placental membrane from the mother to the fetus and that such transfer could lead to altered neuromuscular transmission in the fetus and newborn. However, this observation was discussed with the clinical and maternal health (MH) team to determine if such information would be useful to the clinician for prescribing the product given that the proposed labeling includes human data describing placental transmission of succinylcholine. Therefore, even though the reviewer concurs with the Applicant stance that such information is important, at this point I am not convinced that the information need be included in the PI given the human data.

2. Wiqvist N, Wahlin A. Effect of succinylcholine on uterine motility. Acta Anaesthesiol Scand. 1962;6:71-5

Vertebrate non-striated muscles are categorized into two types: multi-unit muscles/striated and visceral or smooth muscles. The former group includes the nictitating membrane and the muscles in the blood-vessel walls and their conduction is mediated by autonomic nerve fibers. Succinylcholine induces relaxation of these muscles. On the other hand, in smooth muscle organs represented by intestine, ureter

and uterus, conduction is propagated from muscle fiber to fiber. The authors states that very few studies have been made on the effect of succinylcholine on this group (during the time the study has been published). In the published study, the authors wanted to study whether succinylcholine had any influence on the uterine motility and tone in animals and on human subjects.

Spontaneous uterine motility was recorded in vivo in the non-pregnant cat and rat. Anesthetized animals were maintained on a ventilator. The uterus was cannulated with a polythene tube after incision through the midline. The polythene tube was connected with a transducer and the intra-uterine pressure recorded on a Grass instrument. Carotid arteries were cannulated to measure arterial pressure. In humans, pregnant women at the third or fourth month of gestation undergoing legal abortion were included. The amniotic cavity was punctured transabdominally with a needle; a thin polythene catheter was introduced, and the amniotic pressure recorded. In cats, 1-2 mg of succinylcholine in 1 mL Ringer solution did not change the uterine motility. In rats, even a higher dose of 3 mg that was sufficient to cause respiratory arrest did not result in noticeable change in uterine contractility or rhythm (Fig 1).

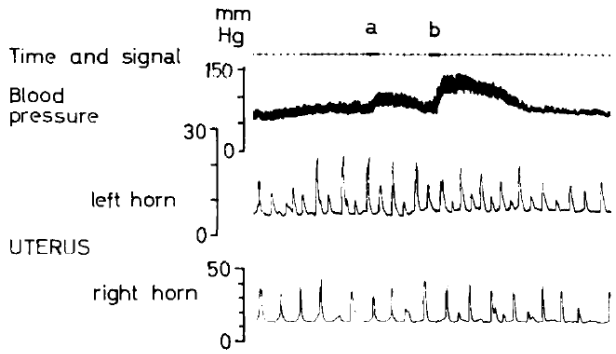

Fig. 1.—Effect of succinylcholine on uterine motility and blood pressure of the non-pregnant rat. Intra-uterine pressure recorded from both horns. Time marking: 30 sec.
a) Intravenous injection of 0.3 ml Ringer solution.
b) Intravenous injection of 3 mg succinylcholine in 0.3 ml Ringer solution.

The authors also concluded that succinylcholine did not have any effect on the human uterus as it did not block the appearance of strong uterine contractions induced by oxytocin.

Reviewer's note: This study was conducted in 1962, which is more than 50 years ago. The setup of the experimental techniques as well as results are pretty straight forward. However, it is not clear to this reviewer how many rats and cats each were used in the study. Moreover, the study lacks some details, e.g., no positive controls were used in the experiment. Therefore, even though the results are intriguing, this reviewer does not find it necessary to include the information in the label. Given the extensive clinical use of the drug, data from humans is more appropriate to inform any labeling recommendations.

10 Special Toxicology Studies

No special toxicology studies were submitted with this NDA.

11 Integrated Summary and Safety Evaluation

NDA 215143 was submitted to seek marketing approval for Succinylcholine Chloride Injection, USP 20 mg/mL, as an adjunct to general anesthesia, to facilitate tracheal intubation, and to provide skeletal muscle relaxation during surgery or mechanical ventilation. The NDA was submitted as a 505(b)(2) application relying on the Agency's previous finding of safety and efficacy of the listed drug QUELICIN™ (succinylcholine chloride injection, USP) approved under NDA 008845 for Hospira, Inc. Since the NDA is a 505(b)(2) application and an adequate scientific bridge was established between this product and the referenced product indicating that exposures are comparable, no new nonclinical studies for succinylcholine were submitted with this NDA or required.

Drug substance impurities and drug product degradants are either within specification limits according to ICH Q3A(R2) and Q3B(R2) guidances, respectively, or their levels can be justified to be safe for human use based on prevailing data for the referenced approved product for the same route and indication. In addition, the detected degradants succinylmonocholine and succinic acid are major human metabolites, and therefore, the specifications are considered adequate.

Although numerous potential leachables including elemental impurities were identified during the extractable study with the container closure system, only 2 organic and 2 USP <232> elemental leachables were found in the long-term stability sample at or above the default reporting limit of (b) (4) mcg/mL. Nevertheless, the maximum levels of these organic compounds and elemental impurities that could be potentially administered daily to humans are not of human safety concern as they are within the permissible daily exposure limits for these organic compounds and elemental impurities.

12 Appendix/Attachments

N/A

References

A. Drabkova, J. Crul, J. F. and Van der Kleijn, E. Placental transfer of 14C-labeled succinylcholine in near term Macaca mulatta monkeys. Br J Anaesth. 1973;45(11):1087-96.
B. Wiqvist N, Wahlin A. Effect of succinylcholine on uterine motility. Acta Anaesthesiol Scand. 1962;6:71-5.

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