

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203629Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	1/6/13
<b>From</b>	Christopher D. Breder, M.D. Ph.D. Clinical Team Leader, Anesthetic Drugs Division of Anesthesia, Analgesia and Addiction Products
<b>Subject</b>	Cross Discipline Team Leader Review
<b>NDA/BLA # Supp #</b>	203629
<b>Applicant Name</b>	APP Pharmaceuticals, LLC
<b>Date of Submission</b>	December 28, 2012
<b>PDUFA Goal Date</b>	October 29, 2012 ( 3-MO clock extension to January 29, 2013)
<b>Proprietary / Established (USAN) names</b>	Neostigmine methylsulfate injection (USP) (generic name); No trade name proposed
<b>Dosage forms / strength</b>	Injectable solution / 0.5 mg/ml, 1.0 mg/ml
<b>Proposed Indication(s)</b>	1. Reversal of non-depolarizing neuromuscular blocking agents
<b>Recommended Action:</b>	<i>Approval</i>

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## 1. Introduction to Review / Executive Summary

The applicant, APP Pharmaceuticals, LLC ("APP") has submitted a 505(b) (2) New Drug Application (NDA) application for Neostigmine Methylsulfate Injection, USP for the indication of reversal of non-depolarizing neuromuscular blocking agents. These non-depolarizing neuromuscular blocking agents include, but are not limited to vecuronium, pancuronium, atracurium, rocuronium, cisatracurium and tubocurarine.

This review will provide an overview of the regulatory and scientific facts of this application and issues that were identified during the course of the review of the submission. Aspects that will be touched upon include the regulatory history, the adequacy of the data to support the application, and the labeling requested by the Applicant.

Several issues were noted by the reviewers of this NDA at the time of their original discipline reviews, including:

- Nonclinical
  - Structural alerts for impurities and the parent molecule;
  - Phenol content of the drug product;
  - Extractable / Leachable profile of the container closure system;
- Chemistry Manufacturing Controls (CMC)
  - Unsatisfactory manufacturing and controls for the drug substance; The referenced DMF (b) (4) is found inadequate to support this NDA;
  - The recommendation from the Office of Compliance is "Withhold" based on the findings discussed in this and the primary CMC review;
  - Incomplete environmental assessment;
  - Unsatisfactory specifications for total impurities in the drug product;
- Clinical
  - Satisfactory definition of the efficacious dose range and the labeling to describe it.

In the time interval between the completion of the individual discipline reviews and the completion, all of these issues have been resolved to the satisfaction of the disciplines and are clarified in addenda or additions to the original reviews, except the issue of inspection of the manufacturing facility (**see Section 3.1.2**).

I have made a minor recommendation to amend the lower dose in Dr. Simone's proposed dosing range from 40 to 30 mcg/kg (see discussion in **Section 3.5.2.2**). This change is reflected in the proposed labeling, which Dr. Simone is in agreement.

Accordingly, I recommend approval of the application pending satisfactory resolution of the inspection issues.

## 2. Background

### 2.1. **Scientific and Clinical Background**

*Adapted from the primary clinical review of Dr. Simone, MD PhD*

#### **Scientific Background**

Neostigmine, an anticholinesterase agent first synthesized in 1931, competes with acetylcholine for binding to acetylcholinesterase and thereby inhibits the hydrolysis of acetylcholine at sites of cholinergic transmission. At neuromuscular junctions, the neostigmine-induced reduction in the breakdown of acetylcholine facilitates neuromuscular transmission. Clinically, this effect of neostigmine has been used for the treatment or prevention of post-operative non-obstructive abdominal distention, i.e., adynamic ileus, the symptomatic treatment of myasthenia gravis and the reversal of nondepolarizing neuromuscular blocking agents (NMBAs).

The proposed clinical use of neostigmine, i.e., reversal of neuromuscular blockade due to the administration of nondepolarizing blocking agents, is predicated on its pharmacological action. Specifically, nondepolarizing NMBAs induce paralysis by competing with acetylcholine at the postjunctional nicotinic receptors where they prevent changes in ion permeability of the skeletal muscle endplate and thereby prevent depolarization and subsequent contraction. Neostigmine, by inhibition of acetylcholinesterase, increases the amount of acetylcholine at the junction, which can compete with the NMBA and ultimately restore impulse transmission and skeletal muscle function.

Neostigmine is associated with direct postsynaptic cholinomimetic effects that may be severe enough to warrant treatment with an anticholinergic agent such as atropine or glycopyrrolate. As the neostigmine-induced inhibition of acetylcholinesterase is fully reversible, in contrast to organophosphates, its cholinomimetic effects have limited duration.

#### **Clinical Background**

In general, the goal in reversing an NMBA is to expedite and assure the return of neuromuscular function to the extent that a patient is capable of maintaining a patent airway and an adequate level of ventilation so that mechanical ventilation can be discontinued and the trachea extubated. In the clinical practice of anesthesia, a number of assessments are typically made to evaluate a patient's ability to carry out both of these functions. These assessments include:

- Mechanical responses of muscles to electrical stimulation of the motor nerves supplying them,
- Grip strength, which requires a level of consciousness that permits the patient to follow commands,

- Sustained head lift, for 5 or more seconds, which requires a level of consciousness that either allows the patient to follow commands or is associated with a return of the gag reflex,
- Spontaneous ventilation parameters, such as
  - Negative inspiratory force > -20 cm H<sub>2</sub>O
  - Tidal volume > 5 mL/kg
  - Vital capacity > 10 mL/kg
  - Respiratory rate < 30 breaths/min
  - Appropriate oxygen saturation and end-tidal CO<sub>2</sub> levels

The clinical benefit of neostigmine lies in its ability to substantially reduce the recovery time from NMBAs. No clinical studies have been reported in the literature demonstrating a meaningful benefit for the reductions in recovery times observed with neostigmine. However, several potential benefits can be postulated and may be reasonably incorporated into the benefit risk analysis. These include reducing the risks associated with:

- Patient movement during the final stages of the surgical procedure including wound closure because the ability to reverse an NMBA permits maintaining paralysis through the end of surgery.
- Exposure to anesthetic agents required to maintain unconsciousness as they may be discontinued once paralysis has been reversed.
- Mechanical ventilation and the presence of an endotracheal tube as well as other airway management devices as they can be discontinued with return of spontaneous ventilation and maintenance of a patent airway.
- Delays in evaluation of neurological function, i.e., assess a patient's ability to move extremities, peripheral sensation, speech or cognitive function, following certain surgical procedures that can affect the nervous system, e.g., spine surgery, carotid endarterectomy.

## 2.2. ***Regulatory History***

*Adapted from the primary clinical review of Dr. Simone*

Neostigmine was first approved by the FDA in 1939 as Prostigmin® (NDA 654). The regulatory status of previous NDAs for various formulations of neostigmine is found in **Table 1**.

**Table 1 Regulatory Status of Previous NDAs for Neostigmine**

NDA#	Drug Name	Division	Strength (route)	Marketing Status	AP Date	Indication	Company
654	Prostigmin (Neostigmine bromide 5%) ophthalmic solution	DAIP	5% (ophthalmic)	Approval was withdrawn in 1995	1939	Glaucoma	Valeant Pharmaceuticals International
2449	Neostigmine methylsulfonate & Atropine sulfate	Unknown	1.5 mg/mL & 0.6 mg/mL (Injection)	Discontinued in 1954	5/9/1940	Intestinal peristalsis stimulant and diagnostic for Myasthenia gravis & related disorders	Hoffman-La Roche, Inc.
2574	Morphine sulfate & Neostigmine methylsulfonate	Unknown	8 mg morphine & 0.5 mg Neostigmine (hypodermic tablet)	Discontinued 1948	6/4/1940	Analgesic/ local anesthetic	Hoffman-La Roche
2575	Hydrochlorides of opioid alkaloids & Neostigmine methylsulfonate	Unknown	0.5 mg (hypodermic tablet)	Approved but never marketed; withdrawn?	6/13/1940	Analgesic	Hoffman-La Roche

(b) (4)

### 2.3. **Current Submission**

The Division met with the Applicant on December 22, 2009, to discuss the information that would be necessary to file an NDA. The meeting package was submitted under PIND 106574. The key discussion points of the meeting are summarized below.

#### **CMC Issues**

1. To support the shelf life of the product the following points were made:
  - a. Real-time data, obtained from testing only at 25 ± 2° C, 60 ± 5% relative humidity (RH) through 6 months, and accelerated data, obtained from testing at 40 ± 2° C, 75± 5% RH through 6 months may be acceptable for filing, but might not support a shelf life of 24 months.
  - b. Expiration dating will be assessed as per ICHQ1E during the NDA review and will be based on available real time primary and supporting stability data and statistical analysis evaluation, if applicable.

- c. It was strongly recommend that the maximum available stability data for the primary stability batches be provided at the time of NDA submission as data submitted afterwards may not be reviewable within the time allotted by GRMP.
2. The following were also to be provided in the NDA submission:
  - a. Photostability data, as per ICHQ1B,
  - b. Data on physicochemical compatibility with atropine, other coadministered drugs and diluents,
  - c. Data on particulates, neostigmine assay and levels of impurities/degradants,
  - d. If the stability data for the registration and stability lots can be statistically pooled and support a 24-month shelf life, a 24-month shelf life may be requested in the NDA submission provided the formulation of the proposed drug product is the same as the currently marketed product and that the formulation and container closure system of the drug product in the marketing application are identical to the currently marketed product.
  - e. Expiration dating will be determined during the NDA review and will be based on ICH Q1E (Evaluation of Stability Data) requirements.
  - f. An in vitro physicochemical compatibility study should be conducted assessing the combinations of neostigmine and atropine and neostigmine and glycopyrrolate as these two anticholinergics are frequently mixed in the same syringe in clinical practice.
  - g. A specification for osmolality for the drug product will need to be provided in the NDA.
  - h. A list of all manufacturing and testing facilities, in alphabetical order, a statement about their cGMP status and whether they are ready for inspections at the time of NDA submission will need to be provided in the NDA submission. In addition, for each manufacturing site, a contact name, telephone number, facsimile number and email address will need to be provided along with specification of the responsibilities of each facility in the manufacturing process. Specification as to which sites are intended to be primary and which are to be alternate sites of production needs to be made.
  - i. Facilities with unacceptable cGMP compliance may jeopardize the approvability of the NDA.

### **Nonclinical Issues**

1. The Division indicated that if the drug product contains impurities, degradants, or leachables which exceed generally allowable levels and are not qualified for safety, it may be necessary to demonstrate that the proposed to-be-marketed product will not expose the public to a less safe version of neostigmine than other products currently found on the market. It was specifically noted that any impurity or degradation product that exceeds ICH thresholds may need to be adequately qualified for safety as per ICHQ3A(R) and ICHQ3B(R) at the time of NDA submission. Adequate qualification would include:

- a. Minimal genetic toxicology screen (two in vitro genetic toxicology studies) with the isolated impurity tested up to the limit dose for the assay,
  - b. Repeat dose toxicology of appropriate duration to support the proposed indication,
  - c. Any impurities or degradation products that contain structural alerts for mutagenicity may be held to more stringent standards of control.
  - d. Impurities greater than the ICHQ3B threshold can potentially be justified for the NDA through comparison against currently marketed products as can excipients provided the levels and duration of exposure for each are the same as or exceed that of neostigmine when administered at the proposed doses.
4. The Division also noted that neostigmine does not appear to have information related to genetic or reproductive toxicology to inform the product label. While normally required for approval, these studies will not be required pre-approval but would be Post-Marketing Requirements unless sufficient data is provided to address these concerns and allow for adequate labeling.
  5. Submission of two exhibit batches for each of the two strengths of Neostigmine Methylsulfate Injection, USP would be sufficient to support a 505(b) (2) marketing application provided impurities and degradants are monitored and reported as per ICHQ3B. For impurities that contain a structural alert for mutagenicity, appropriate assay(s) will be needed to detect these substances at levels called for in ICHQ2.

#### **Clinical Pharmacology Issues**

6. All available Clinical Pharmacology information related to pharmacokinetics, distribution, metabolism, elimination, dose-response, and special populations (such as drug-drug interactions, hepatic impairment, renal impairment, elderly, gender, pediatrics, etc) needs to be summarized in the NDA. All aspects of Clinical Pharmacology information included under the Physician Labeling Rule for the content of the clinical pharmacology section of the label need to be addressed.
7. In the absence of PK studies conducted with the to-be-marketed formulation, a biowaver will be required as per 505 (b)(2) regulations. The waver request can be restricted to the proposed indication and route of administration and may be justified by providing evidence that the to-be-marketed formulation was used in the PK or clinical studies cited in the literature. If the PK or clinical literature articles did not use the to-be-marketed formulation, then an effort should be made to relate the formulations used in the clinical literature to the to-be-marketed formulation.

#### **Clinical Issues**

8. The clinical information for the NDA was to be obtained solely from the published literature.
  - a. The Division indicated that each published study should be critically reviewed and its data organized to allow an organized assessment of efficacy and safety.
  - b. The Division also indicated that the safety data should be integrated, to the extent possible, to create a safety database that can be analyzed according to

- subject demographics, dose of neostigmine evaluated, use of an anticholinergic, and neuromuscular blocking agent reversed. The efficacy data should be integrated according to the same parameters as the safety data.
- c. The Applicant indicated that they believed there were sufficient data from well-designed, randomized, blinded, controlled studies to support a finding of safety and efficacy. The Division indicated that this would be a review issue and that the Applicant should make a good faith effort to acquire protocols and the original clinical data from the studies.
9. The Applicant sought approval of neostigmine only for the reversal of neuromuscular blocking agents (b) (4)
- 
- a. The safety analyses should focus on patients receiving neostigmine for the indication of reversal of the neuromuscular blocking effects of nondepolarizing muscle relaxants. However, the safety of neostigmine when used for other indications should also be included in the NDA, but should be easily identified as such; the safety analyses should be conducted with and without the supporting safety data.
10. The Division stated that the approach taken for the pediatric patient population PK, safety and efficacy data should be similar to that used for the adults and that information for each of these should be provided for each of the pediatric subpopulations:
- a. Neonate (< 1 month)
  - b. Infant (1-24 months)
  - c. Child (pre-school) (2-6 years)
  - d. Child (school-age) (6-12 years)
  - e. Adolescent (12-16 years)

Furthermore, critical information that was not found or not adequately addressed in the literature would need to be supplemented by clinical trials in this patient population.

### 3. Synopsis of Discipline Reviews

#### 3.1. **CMC/Microbiology/Device**

*Adapted from the primary clinical review of Dr. Jao, PhD*

##### 3.1.1. Review Strategy

The initial chemistry review of this NDA was completed 9/17/12 by Dr. Jao, ONDQA/Division III/Branch VIII and then signed by Dr. Prasad Peri, PhD The recommendation of ONDQA was for a Complete Response (CR; see the following

section for discussion). A second Review was submitted 12/21/12 to discuss resolution of the deficiencies leading to the initial CR recommendation.

### 3.1.2. General Product Quality Considerations

The following deficiencies were noted in Dr. Jao's first review and culminated in his recommendation for a complete response from a CMC perspective.

1. The applicant of the NDA has provided insufficient information to assure the identity, strength, purity, and quality of the drug product. Specifically, the manufacturing and controls for the drug substance are unsatisfactory. The referenced DMF (b) (4) is found inadequate to support this NDA.
2. The recommendation from the Office of Compliance for this NDA is "withhold".

During the 6/13 – 7/8/11 inspection of the APP manufacturing facility located at 3159 Staley Road, Grand Island, New York, 14072-2028, investigator(s) from the Food and Drug Administration (FDA) New York District identified the following:

- Significant violations of Current Good Manufacturing Practice (CGMP) regulations for Finished Pharmaceuticals according to [21 U.S.C. § 351(a)(2)(B)].
- Violation of 21 U.S.C. §§ 331(d) and 355(a) for manufacturing prescription drugs without an approved application
- Failure to submit NDA Field Alert Reports (FARs) to FDA in compliance with 21 C.F.R. § 314.81 (b)(l)(ii), as required by section 505(k) of the Act [21 U.S.C. § 355(k)].

The firm supplied a response of 07/29/11, but it was determined by the Agency to lack sufficient corrective actions. A Warning Letter (NYK-2012-14) was sent to the Sponsor 2/22/2012.

3. Complete the environmental assessment.
4. Tighten the acceptance criterion of NMT (b) (4) % for total impurities in the drug product to NMT (b) (4) % to be reflective of data.

The statuses of the above deficiencies at the time of Dr. Jao's second review (12/21/12) are as follows:

1. The holder of DMF (b) (4) has satisfactorily addressed all the CMC issues, except the formal submission of the drug substance specification to include controls for residue (b) (4), which has been found to below (b) (4) ppm (LOD) for more than 10 batches currently manufactured. Once the specification for the drug substance is formally updated by the DMF holder, they will inform the NDA holder to update the receiving specification. The initial request of tightening the acceptance criterion of NMT (b) (4) % for total impurities in the drug product to NMT (b) (4) % was not pursued from the risk management perspective.

- There are no other pending CMC issues for the drug substance and drug product.
2. Even though this drug product has been marketed in US, it has never been approved for its intended use. In his first review, Dr. Jao noted that Dr. Raanan Bloom, the OPS Environmental Officer, recommended that the applicant submit a categorical exclusion request under 21 CFR 25.31(b) or an Environmental Assessment if introductions are above 1 ppb, regardless of the marketing history of this drug product. The applicant submitted the environmental assessment on 9/20/2012, which was reviewed and considered acceptable by Dr. Raanan Bloom.
  3. The recommendation from the Office of Compliance for this NDA remains as "withhold". The manufacturing site was supposed to have been reinspected by late December but at the time of this review, it has not taken place<sup>1</sup>.

In conclusion, this NDA is recommended for approval from the ONDQA perspective, pending on the final recommendation from the Office Compliance.

### 3.2. **Nonclinical Pharmacology/Toxicology**

*Adapted from the primary review of Dr. Hao, PhD and secondary review of Dr. Mellon, PhD.*

#### 3.2.1. Review Strategy

The primary pharmacology toxicology review was completed by Dr. Hao and the secondary review by Dr. Mellon ("the Nonclinical Team"; NCT).

The NDA was received by the NCT on December 29, 2011. No new nonclinical studies were submitted at that time. Two study reports, an in vitro mutagenicity study for neostigmine (b) (4)

The published literature component of the Nonclinical submission consisted of studies describing the pharmacodynamic effects of the drug. There were no published studies that could be described as adequate acute or repeat-dose toxicology studies, genetic toxicology studies, or reproductive and developmental toxicology studies that could be used to provide nonclinical safety support or inform the labeling.

#### 3.2.2. General nonclinical pharmacology/toxicology considerations

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<sup>1</sup> Personal communication with Dr. Peri Prasad on 12/28/12

As discussed in the 2009 preIND meeting with the Sponsor (see Section 2.2), no new nonclinical pharmacology or toxicology studies for the drug substance were required to support approval of this NDA given the long clinical history of neostigmine use. The pharmacology toxicology review focused on three main nonclinical review issues identified by Dr. Hao in her review of this submission: (1) drug substance impurities with structural alerts for mutagenicity, (2) safety justification for the levels of the excipient phenol in the drug product, and (3) potential leachables/extractables from the container closure system due to the presence of phenol in this drug product formulation. As noted in her reviews, adequate data were available to support the safety of the container closure system, the drug substance impurity specifications, and the drug product degradant specifications. Each of these will be summarized below.

#### 1) Drug Substance Impurities

The Sponsor did not specifically discuss the potential for structural alerts in the drug substance impurities or the parent; rather they proposed to follow the current USP specifications. Upon review of the structures, the NCT noted that all of the potential impurities contain structural alerts for mutagenicity; In fact, neostigmine itself contains structural alerts for mutagenicity. NCT requested a computational toxicology Qualitative Structure Activity Relationship (QSAR) evaluation, which is reproduced in the Appendix of Dr. Hao's first review. As she noted, all of the impurities were predicted to be positive in the Ames assay and one of the compounds actually has been reported to be positive in this assay. The lack of data for neostigmine and the structural alerts identified was discussed with the Sponsor in a teleconference on April 13, 2012. As there were no genetic toxicology data for neostigmine alone, and similar, if not identical, chemical moieties in the impurities are also in the parent, the NCT recommended that the Sponsor either tighten the specifications to result in exposure of NMT 1.5 mcg/day or conduct an Ames assay to determine if the impurities were genotoxic or not. At the current specifications, a person would be exposed to (b) (4) mcg/day of potentially genotoxic impurities that presumably do not contribute to the efficacy of the drug product and therefore only contribute risk. It is likely that these impurities are present in the currently marketed unapproved drug product supplied by APP. After evaluation of the information, the Sponsor indicated that they would pursue qualification via genetic toxicology data and submit the studies in August of 2012. On August 29, 2012, Ames assays for both neostigmine drug substance and drug product were submitted. In her review of these studies, Dr. Hao concluded that neostigmine did not demonstrate evidence of mutagenic potential.

#### 2) Phenol levels

The concentration of phenol in this drug product is less than other FDA-approved intravenous drug products and the total daily dose of intravenous phenol is also less than other FDA-approved intravenous drug products. From that perspective, the NCT stated that phenol is not novel. However, they noted that in all other identified FDA-approved drug products, the drugs are administered several times a day rather than as a single bolus injection. Therefore, the use of phenol in this drug product is novel in

the sense that it likely results in a higher  $C_{max}$  than any other identified drug product to date.

There are no intravenous toxicology studies for either phenol or this neostigmine formulation; therefore, there are technically inadequate data to justify the safety of the proposed bolus dose of phenol. However, the Division recognizes that this formulation has been marketed by APP for over 20 years, and considerable human experience appears to exist which may be deemed adequate upon review to justify the safety of the phenol in this drug product formulation.

### 3) Container closure

In the preIND meeting held in 2009 (see Section 2.2), the Division specifically noted that APP should provide adequate justification for the safety of the container closure system of this drug product. APP did not include a new leachable/extractable assessment for the container closure in the original NDA submission; rather they noted that a (b) (4) gray (b) (4) rubber serum stopper provided by (b) (4) has been used in many other aqueous drug products. Upon initial review, we were concerned that the phenol will alter the leachable profile and therefore, requested that an extractable/leachable study be completed and a toxicological risk assessment for the identified leachables be provided to support the safety of the container closure. This was communicated in the 74-day letter and the Sponsor originally indicated that the study results would be provided by July 31, 2012. In a communication from the Sponsor dated July 30, they noted that the study results would be submitted by August 31, 2012. During the course of the review, Dr. Hao was able to identify two other FDA-approved intravenous generic drug products that also contain (b) (4) % phenol and use the same (b) (4) stopper in their container closure system. Therefore, since the Agency appears to have approved other intravenous phenol-containing drug products that employ the same container closure system, we cannot consider this an approval issue for this NDA at this time. (b) (4)



(b) (4)

(b) (4)

As we have been able to identify at least two ANDAs for intravenous drug products that were approved by the Office of Generic Drugs that also contain phenol, the lack of an adequate extractable/leachable risk assessment cannot be deemed an approval issue. Nonetheless, the concern that the phenol may result in increased leachables over time remains and there do not appear to be adequate data by current standards to address this issue. Therefore, I concur with Dr. Hao that the Sponsor should provide an adequate extractable leachable study as a PMR.

### 3.2.3. Carcinogenicity

This issue is discussed in **Section 3.2.2**. PMRs for genetic toxicity were requested, however, further animal studies were not required to evaluate the potential for carcinogenicity because the drug is not intended for chronic use.

### 3.2.4. Reproductive toxicology

No reproductive and developmental toxicology data for neostigmine from original studies or the published literature were submitted to inform product labeling. Given the long clinical experience with neostigmine for the proposed use, the NCT deemed these studies acceptable as post-marketing requirements. I concur with this position.

### 3.2.5. Other notable issues (resolved or outstanding)

Based on the data submitted to date, the following studies are recommended by the NCT as PMRs should this NDA be approved:

1. Conduct an in vitro or in vivo assay using mammalian cells for chromosomal damage for neostigmine methylsulfate.
2. If you conducted an in vivo assay to address number 1 above, conduct a second in vivo assay for chromosomal damage for neostigmine methylsulfate; otherwise conduct an in vivo assay for chromosomal damage for neostigmine methylsulfate. PMRs 1-2, you may refer to the options outlined in ICH S2(R1) titled "Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use" and propose an adequate battery of genetic toxicology studies.
3. Conduct a fertility and early embryonic development toxicology study in the rat model for neostigmine methylsulfate.
4. Conduct an embryo-fetal developmental toxicology study using the rat model for neostigmine methylsulfate.
5. Conduct an embryo-fetal developmental toxicology study using the rabbit model for neostigmine methylsulfate.
6. Conduct a peri- and post-natal developmental toxicology study in the rat model for neostigmine methylsulfate.
7. Conduct an adequate extractable/leachable safety assessment for the (b) (4)

(b) (4) gray (b) (4) rubber stopper used in your container closure system. This assessment must include controlled extraction studies to qualitatively and quantitatively determine the chemical species which may migrate into the dosage form using appropriate solvents that adequately represent the chemical characteristics of the drug product formulation, and leachable data from long-term stability studies (taking into consideration the proposed shelf-life) to determine if the identified/specified extractables also leach into the drug product over time, and a toxicological risk assessment justifying the safety of the extractables and leachables taking into consideration the maximum daily dose of the identified materials for this drug product. For your toxicological risk assessment, any leachable that contains a structural alert for mutagenicity should not exceed 1.5 mcg/day total daily exposure or be adequately qualified for safety. A toxicological risk assessment should be provided for any non-genotoxic leachable that exceeds 5 mcg/day.

### 3.3. **Clinical Pharmacology/Biopharmaceutics**

*Adapted from the primary review of Dr. David Lee, PhD*

#### 3.3.1. Review Strategy

The Clinical Pharmacology primary review was performed by Dr. Lee and signed off without comment from Dr. Yun Xu, PhD.

The Applicant submitted 8 and 5 publications under clinical pharmacology and biopharmaceutics (assay methodology), respectively. A cursory review was conducted by the Applicant and presented as below in a table format. All publications were reviewed by Dr. Lee based on the current review practice. In particular, study design, dosage administration, blood sampling scheme, and analytical methodology information were focused during the review.

#### 3.3.2. General clinical pharmacology/biopharmaceutics considerations

Dr. Lee presented the following table that summarized the clinical pharmacology findings as presented by the applicant:

**Table 2 Clinical Pharmacology findings presented by the Applicant**

Author	Treatment		PK parameters			
	Neo	Other meds	C <sub>max</sub> , T <sub>ax</sub> , AUC	T <sub>1/2</sub> (min)	CL (mL/min/kg)	V <sub>d</sub> (L/kg)
Williams	Neo methylsulfate 5 mg iv	Atropine sulfate 1.2 mg iv	Conc. profile	24	Not reported	6.2
Chan (Analytical method)	Neo bromide 5 mg iv	Not reported	Conc. profile	Not reported	Not reported	Not reported
De Ruyter (Analytical method)	Neo 0.05 mg/kg	Not reported	Conc. profile	Not reported	Not reported	Not reported
Fisher De Ruyter method	Infants 100 µg/kg iv Children and adults 70 µg/kg iv	Atropine 30 µg/kg iv	Conc. profile	Infants: 39 Children: 48 Adults: 67	Infants: 13.6 mL/min/kg Children: 11.1 Adults: 9.6	Infants: 0.08 Children: 0.09 Adults: 0.04
Calvey	Neo methyl 68.9-103 µg/kg iv	Atropine sulfate 1.2 mg iv	Conc. profile	25.4	5.72	0.12
Morris De Ruyter method	Neo methyl 70 µg/kg iv	Atropine sulfate 1.0 mg iv	Not reported	a=3.4 b=77	9.2	0.74
Broggini Authors' own HPLC method	Neo 0.5 mg iv	Not reported	C <sub>max</sub> : 8.84 T <sub>max</sub> : 0.08 h AUC=126.8 (ng.h/mL)	1.88 h or (112.8 min)	0.7 L/h/kg	0.18 MRT 2.83 h
Cronnelly Chan method	Neo 70 µg/kg iv	Atropine 0.03 mg/kg iv	Conc. profile	Normal: 79.8 Anephric: 181.1 Transplant: 104.7	Normal: 16.7 Anephric: 7.8 Transplant: 18.8	Normal: 1.4 Anephric: 1.6 Transplant: 2.1

Dr. Lee determined that all of the publications submitted in the application do not have adequate analytical information (e.g., QCs, recovery, stability, validations, etc.). According to his review, based on the current clinical pharmacology standards, none of the publications are adequate and are not optimal in presenting the information needed for the Labeling purpose. However, it appears to him that the following information (**Sections 3.3.2.1 - 3.3.2.3**) is consistent throughout the publication regardless which analytical methods used.

### 3.3.2.1. Drug-drug interactions

Dr. Lee noted that the pharmacokinetic interaction between neostigmine and other drugs has not been studied. He advised that since neostigmine is metabolized by microsomal enzymes in the liver, one should use with caution when using neostigmine with other drugs which may alter the activity of metabolizing enzymes or transporters.

### 3.3.2.2. Metabolism and Pathway of Elimination

- Neostigmine half life ranged from 77 to 113 minutes after a single intravenous administration.
- Nonclinical information suggested that neostigmine is eliminated in the urine and feces (unabsorbed material given by routes other than IV) unchanged and undergoes hepatic metabolism in the liver microsomes. 3-Hydroxyphenyltrimethyl ammonium (PTMA) is the primary metabolite, which then becomes glucuronide conjugated PTMA.

### 3.3.2.3. Demographic interactions/special populations

#### Age – Elderly

The only significant difference between the young and elderly was initial volume of distribution (V1), which was lower in the elderly. Numerically the clearance in elderly ( $23.4 \pm 4$  mL/kg/min) is also lower compared to younger patients ( $33.5 \pm 4$  mL/kg/min). Overall the duration of maximum response to neostigmine was significantly prolonged in the elderly ( $42 \pm 10$  minutes) compared to the younger group ( $13.14 \pm 2.4$  minutes).

#### Age – Pediatrics

From a study by Fisher et al, Dr. Lee noted elimination half-life for infants, children and adults were  $39 \pm 5$  min,  $48 \pm 16$  min, and  $67 \pm 8$  min (mean  $\pm$  SD), respectively. Clearance for infants (2-10 months), children (1-6 years), and adults (29-48 years) were  $13.6 \pm 2.8$ ,  $11.1 \pm 2.7$  and  $9.6 \pm 2.3$  mL/min/kg (mean  $\pm$  SD), respectively.

#### Renally Impaired

From his review, Dr. Lee determined that clearances for normal, transplant and anephric patients were  $16.7 \pm 5.4$ ,  $18.8 \pm 5.8$  and  $7.8 \pm 2.6$  mL/min/kg (mean  $\pm$  SD), respectively. The clearance in patients with impaired renal function is lower compared to patients with normal renal functions. Use with caution in patients with impaired renal functions.

#### Hepatically Impaired

The pharmacokinetics of neostigmine in patients with hepatic impairment has not been studied. Dr. Lee noted that since neostigmine is metabolized by microsomal enzymes in the liver, caution should be exercised with the use in patients with impaired hepatic functions.

### 3.3.3. Biopharmaceutics

During a pre-IND meeting held on 12/22/09, the Agency stated that the Applicant may submit their NDA based the literature information, including to support a biowaiver request, pending the formulations used in the literature are appropriate for reference. Specifically, the Agency stated that “the formal review of submitted information in the NDA application will determine the adequacy of literature to support

a request to waive pharmacokinetic/bioavailability studies for the proposed adult and pediatric subjects.” Therefore, the Applicant requested to waive in vivo pharmacokinetic / bioavailability studies. With respect to bioavailability/bioequivalence requirement as per the 21 CFR320, there are no concerns due to the fact that 1) the bioavailability is “self-evidence” since the Applicant’s formulation is for intravenous use; and, 2) that the Applicant and intravenous formulations described in the literature (based on the descriptions provided in the publications, e.g., neostigmine, preservatives (phenol) and saline) appear to be simple solutions.

### 3.3.4. Thorough QT study or other QT assessment

No information was submitted to characterize neostigmine effect on the QT interval. There did not seem to be a signal from the postmarketing surveillance investigation or from the literature reviewed by Dr. Simone or Martin Pollock (**see Sections 3.5.3.3.3.6, 3.5.3.3.6.1.2, and 3.5.3.3.6.1.3**). Inasmuch as the Clinical Pharmacology group did not believe this to be a deficiency requiring further study before or after approval, I concur with this position considering the long clinical use without an apparent related safety signal.

### 3.3.5. Other notable issues (resolved or outstanding)

Dr. Lee noted that the information submitted in the NDA is acceptable, pending agreement on the labeling language.

## 3.4. **Clinical Microbiology**

*Adapted from the primary review of Dr. Vinayak Pawar, PhD.*

### 3.4.1. Review Strategy

The Microbiology review was performed by Dr. Pawar and signed off in concurrence by Dr. John W Metcalfe, PhD.

### 3.4.2. General considerations

#### 3.4.2.1. Discussion of primary and secondary reviewers’ comments and conclusions

No deficiencies were noted from a Clinical Microbiology perspective. The following aspects of the submission were noted as being acceptable:

- a validated (b) (4) process for containers and closures;
- qualification/requalification of (b) (4)
- acceptable component/equipment (b) (4) (b) (4) qualification/requalification list;

- list (1998- 2011) of acceptable (b) (4) qualification/requalification;
- samples meet acceptance criteria established for USP Antimicrobial Preservative Effectiveness Test;
- validated (b) (4) process for containers and closures;
- the stability testing program supports the drug product's microbiological quality throughout its shelf life; and
- the suitability of sterility and endotoxins test methods at release and the acceptance criteria.

#### 3.4.3. Notable issues (resolved or outstanding)

The reviewer noted that a (b) (4) & preserved multiple dose vial product and no labeling issues pertaining to sterility were identified with this product.

### 3.5. **Clinical/Statistical**

*Adapted from the primary reviews of Dr. Arthur Simone, MD PhD (Clinical) and David Petullo, MS (Statistical)*

#### 3.5.1. Review Strategy – Overall

The Clinical primary review was performed by Dr. Simone and signed off without comment by me. Unless otherwise indicated, the data and views in the Clinical/Statistical part of this review were derived from Dr. Simone's primary review.

As reviewed by Dr. Simone, the literature submitted to the application was selected from the published study reports identified by two literature searches, one conducted in July 2011 and the other in May 2012. The Applicant conducted these searches through the PubMed web-based portal at <http://www.ncbi.nlm.nih.gov/sites/entrez> using the verbatim title search term "neostigmine." Additional filters included "humans", "clinical trials", and "English text only". The date range, for the May 2012 search, was set for the past ten years, which also included the published literature since the cutoff for previous literature searches (July 2011). The reports from both literature searches were analyzed by the Applicant for safety and efficacy. Neither the original protocols nor the raw data from any of these studies were requested or obtained by the Applicant. A full description of the results including those articles excluded by the applicant is included in Dr. Simone's review.

The literature submitted by the Applicant was summarized and evaluated for efficacy in two ways: first, to assess whether neostigmine is efficacious at reversing NMBA-induced paralysis and second, to determine at what point following NMBA discontinuation (e.g., at a T1 of 0.1 or at some designated time point) and at what

dose neostigmine should be administered to effectively reverse the neuromuscular blockade.

Mr. Petullo's statistical review is discussed in **Section 3.5.2.1.2.1**.

### 3.5.2. Efficacy

#### 3.5.2.1. Phase 3/ clinical studies essential to regulatory decision

The publications submitted in support of efficacy were screened based on whether they described controlled studies. Controlled studies in which spontaneous recovery, placebo, or the approved reversal agents edrophonium and pyridostigmine were a comparator, were considered as providing meaningful efficacy data. Studies in which multiple doses of neostigmine were evaluated and those in which the timing of administration of a fixed dose of neostigmine was varied were also considered as providing meaningful efficacy data.

The Applicant did not identify any of these studies as pivotal or perform any efficacy analyses of the studies or the data contained within them. For the purposes of this review, Dr. Simone identified 11 studies reported in the literature that can be considered as pivotal, i.e., prospective, randomized, controlled studies involving recovery of the ToF ratio to 90% (**Table 3**).

**Table 3 Studies considered by the Primary Medical Reviewer to be Pivotal in the Review of NDA 203629<sup>2</sup>**

Source	NMBA Reversed	Dose(s) of Neostigmine (mcg/kg)	Comparator(s)	Study Population
Abdulatif (63)	Rocuronium	5	Spontaneous recovery and a range of neostigmine doses	Pediatric and adult
		10		
		20		
		50		
Baurain (28)	Rocuronium	40	Different neuromuscular blocking agents	Adults
	Vecuronium			
	Atracurium			
	Pancuronium			
Baurain (29)	Vecuronium	20	Doses of neostigmine and timing of administration based on extent of spontaneous recovery	Adults
		40		
		80		
Bevan (41)	Rocuronium	70	Timing of administration based on extent of spontaneous recovery	Pediatric and adult
	Vecuronium	70		
Caldwell (27)	Vecuronium	40	Timing of administration based on time lapsed after vecuronium administration	Adults
Goldhill (17)	Atracurium	15	Spontaneous recovery and a range of neostigmine doses	Adults
		35		
		55		
		75		
Lederer (53)	Rocuronium	30	Spontaneous recovery and two neostigmine doses	Adults
		50		
McCourt (37)	Rapacuronium boluses	50	Spontaneous recovery	Adults
	Rapacuronium infusion			
	Rocuronium			
Melstelman (58)	Vecuronium	30	Timing of administration based on extent of spontaneous recovery	Adults
Sacan (FR)	Rocuronium	70	Edrophonium and sugammadex	Adults
Source	NMBA Reversed	Dose(s) of Neostigmine (mcg/kg)	Comparator(s)	Study Population
Schaller (52)	Rocuronium	5	Placebo and a range of neostigmine doses	Adults
		8		
		15		
		25		
		40		

### 3.5.2.1.1. Subject Disposition

The Applicant did not perform an analysis of subject disposition.

<sup>2</sup> Numbers in parentheses below the author’s names represent the number in the References from Dr. Simone’s review.

### 3.5.2.1.2. Analysis of Primary Endpoint(s)

The Applicant did not perform an analysis of primary endpoints.

The reversal of neuromuscular blockade is most widely assessed, in both clinical practice and clinical research, by assessing the twitch response to a ToF electrical impulses and comparing the ratio of the magnitude of the fourth twitch to that of the first. Furthermore, the ToF ratios that correlate most strongly to a degree of reversal that would allow a patient to maintain and protect a patent airway and adequately ventilate without assistance appear to be those  $\geq 90\%$ . Although most of the older literature has used a ToF ratio of 70% as the standard for assessing adequate reversal, more recent clinical studies have used ratios of 80% and 90%. In the literature, 11 articles described clinical studies assessed recovery to these higher ToF ratios. In the table below (**Table 4**), the findings for those studies are summarized. While these were not combined in an integrated summary by the Applicant, visual inspection of the Table supplied by Dr. Simone suggests that for doses in the range of  $\sim 20$  mcg/kg and higher, adequate reversal (ToF  $\sim 0.9$ ) occurred in a timely manner ( $\sim 10$  min.).

**Table 4 Summary of Key Findings in Pivotal Studies**

Source	NMBA Reversed	Dose of Neostigmine (mcg/kg)	Timing of Neostigmine Administration	Maximum TOF Reported (%)	Time to Maximum TOF (min)	Population
Abdulatif (63)	rocuronium	5	T <sub>1</sub> = 10%	73	10	pediatric
		10	T <sub>1</sub> = 10%	89	10	pediatric
		20	T <sub>1</sub> = 10%	98	10	pediatric
		50	T <sub>1</sub> = 10%	99	10	pediatric
		5	T <sub>1</sub> = 10%	29	10	adults
		10	T <sub>1</sub> = 10%	47	10	adults
		20	T <sub>1</sub> = 10%	62	10	adults
Baurain (28)	rocuronium	40	T <sub>1</sub> = 25%	90	15	adults
	vecuronium	40	T <sub>1</sub> = 25%	88	15	adults
	atracurium	40	T <sub>1</sub> = 25%	92	15	adults
	pancuronium	40	T <sub>1</sub> = 25%	76	15	adults
Baurain (29)	vecuronium	20	T <sub>1</sub> = 10%	76	15	adults
		20	T <sub>1</sub> = 25%	85	15	adults
		20	T <sub>1</sub> = 50%	92	15	adults
		40	T <sub>1</sub> = 10%	86	15	adults
		40	T <sub>1</sub> = 25%	86	15	adults
		40	T <sub>1</sub> = 50%	94	15	adults
		80	T <sub>1</sub> = 10%	80	15	adults
		80	T <sub>1</sub> = 25%	88	15	adults
Bevan (41)	rocuronium	70	T <sub>1</sub> = 1%	90	< 20	pediatric
		70	T <sub>1</sub> = 10%	90	< 20	pediatric
		70	T <sub>1</sub> = 25%	90	< 25	pediatric
		70	T <sub>1</sub> = 1%	90	< 30	adults
		70	T <sub>1</sub> = 10%	90	< 30	adults
		70	T <sub>1</sub> = 25%	90	< 40	adults
	vecuronium	70	T <sub>1</sub> = 1%	90	< 30	pediatric

Source	NMBA Reversed	Dose of Neostigmine (mcg/kg)	Timing of Neostigmine Administration	Maximum TOF Reported (%)	Time to Maximum TOF (min)	Population
		70	T <sub>1</sub> = 10%	90	< 30	pediatric
		70	T <sub>1</sub> = 25%	90	< 30	pediatric
		70	T <sub>1</sub> = 1%	90	< 40	adults
		70	T <sub>1</sub> = 10%	90	< 40	adults
		70	T <sub>1</sub> = 25%	90	< 40	adults
Caldwell (27)	vecuronium	40	TOF = 29%	86	10	adults
Goldhill (17)	atracurium	15	T <sub>1</sub> = 6%	90	16	adults
		35	T <sub>1</sub> = 12%	90	10	adults
		55	T <sub>1</sub> = 15%	90	10	adults
		75	T <sub>1</sub> = 9%	90	10	adults
Lederer (53)	rocuronium	30	5 min. after rocuronium	90	23	adults
		50	5 min. after rocuronium	90	19	adults
McCourt (37)	rapacuronium boluses	50	T <sub>1</sub> = 25%	80	10	adults
	rapacuronium infusion	50	T <sub>1</sub> = 25%	80	9	adults
	rocuronium	50	T <sub>1</sub> = 25%	80	6	adults
Meistelman (58)	vecuronium	30	T <sub>1</sub> = 1%	80	12	adults
		30	T <sub>1</sub> = 10%	100	8	adults
		30	T <sub>1</sub> = 25%	100	5	adults
Sacan (68)	rocuronium	70	T <sub>1</sub> = 12%	90	17	adults
Schaller (52)	rocuronium	5	TOF = 50%	90	9	adults
		8	TOF = 50%	90	5	adults
		15	TOF = 50%	90	4	adults
		25	TOF = 50%	90	3	adults
		40	TOF = 50%	90	2	adults

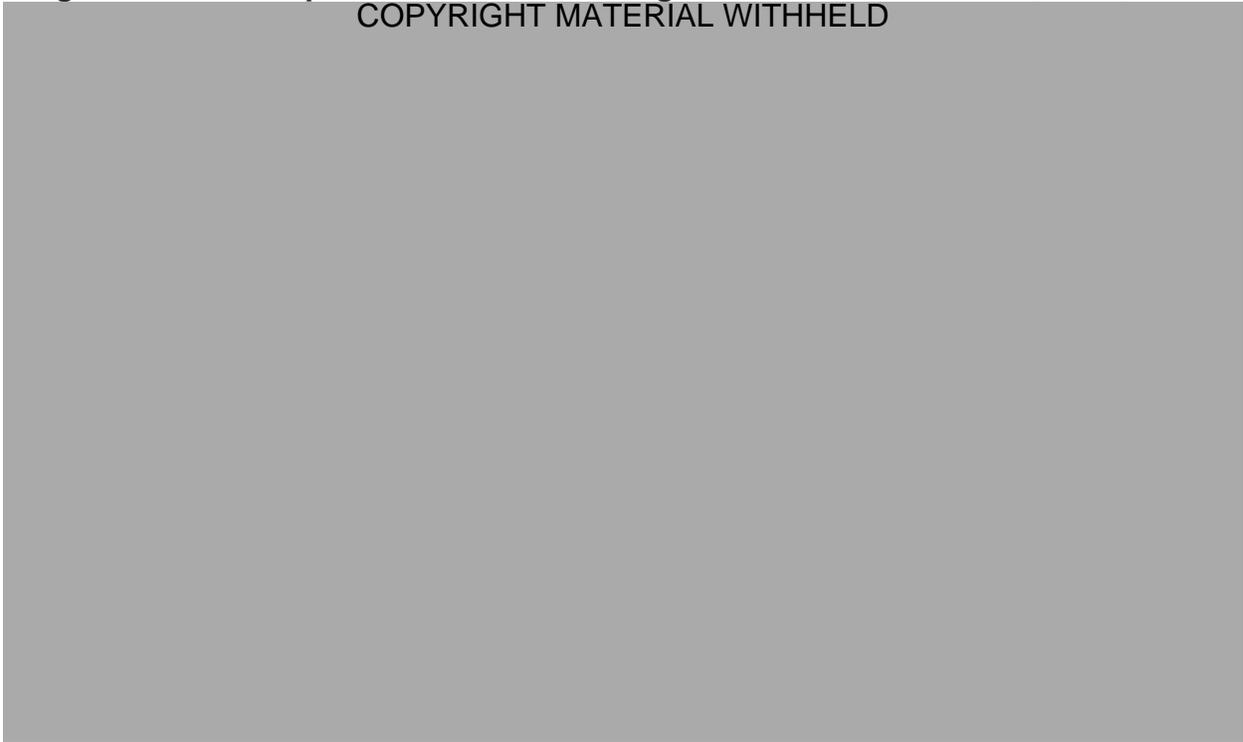
### 3.5.2.1.2.1. Analysis of Primary Endpoint – Statistical Verification

After a preliminary review of the 42 published articles submitted to support the efficacy of neostigmine, Mr. Petullo focused his analysis on the study by Schaller et al., 2010 to determine if there was a difference between the reversal times for neostigmine and placebo in achieving a ToF ratio of 0.9. The values for the sugammadex treatment groups are not of interest and were not to be included in the review.

According to the authors of Schaller et al., the primary aim of this study was to determine the dose of neostigmine and sugammadex which reversed a shallow residual neuromuscular block from a ToF ratio of 0.5 to a ToF ratio  $\geq 0.9$ . In this study, ninety-nine patients were equally randomized to 1 of 11 treatments: sugammadex (0.0625, 0.125, 0.25, 0.5, or 1.0 mg/kg), neostigmine (5, 8, 15, 25, or 40  $\mu\text{g}/\text{kg}$ ), or placebo (saline). A neuromuscular block was applied after induction of anesthesia using rocuronium. When the block was no longer required, spontaneous recovery was allowed until a ToF ratio of 0.5 was achieved. The study drug was then administered according to randomization. The time required to reach a ToF ratio greater than or equal to 0.7, 0.8, and 0.9 was recorded for all patients. The authors reported the median, minimum, and maximum times for each treatment group. There were no comparisons of the recovery times for the individual doses of neostigmine or sugammadex to placebo group as that was not the intent of this study.

The authors presented the individual data points in a dose-response curve for the time to a recovery ratio of 0.9 (**Figure 1**). Three patients were excluded due to major protocol violations, one each in 5, 8, and 40  $\mu\text{g}/\text{kg}$  neostigmine. Since the minimum, median, and maximum times were known, Mr. Petullo approximated the values that were above and below the median but within the reported range by visual examination of **Figure 1**. His approximations, along with the known values, are shown in **Table 5**. He compared each dose of neostigmine to placebo using a log-rank test. Results are shown in **Table 6**.

**Figure 1 Dose Response Curve for Neostigmine based on Schaller, et al., 2010**  
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**Table 5 Time (minutes) for reversal of Neuromuscular Block to ToF Ratio 0.9**

<b>Treatment</b>	<b>n</b>	<b>Time to TOF <math>\geq</math> 0.9 (minutes)</b>
Placebo	9	12, 15.1, 15.5, 16, 19, 22, 23, 27, 33
Neostigmine 5 $\mu$ g/kg	8	5.8, 7, 7.1, 8.3, 10.3, 11.5, 12.1, 15
Neostigmine 8 $\mu$ g/kg	8	3.5, 3.7, 4.0, 5.3, 5.3, 5.5, 6.0, 8.7
Neostigmine 15 $\mu$ g/kg	9	2.8, 3.5, 3.6, 3.9, 4.0, 4.2, 5.1, 5.2, 6.0
Neostigmine 25 $\mu$ g/kg	9	1.7, 2.1, 2.5, 3, 3.2, 4.9, 5, 5.8, 6.2
Neostigmine 40 $\mu$ g/kg	8	1.7, 1.8, 1.8, 2.0, 2.0, 2.8, 2.8, 4.2

Source: Reviewer

**Table 6 Comparison of Time to a ToF  $\geq 0.9$  Approximated from the Schaller et al., 2010 Reference**

Treatment	Time to TOF $\geq 0.9$ (minutes)		p-values*	
	Median	Range	raw	Sidak
Placebo	19	[12,33]	-	-
Neostigmine 5 $\mu\text{g}/\text{kg}$	9.3	[5.8, 15]	0.01	0.07
Neostigmine 8 $\mu\text{g}/\text{kg}$	5.3	[3.5, 8.7]	<0.0001	0.0001
Neostigmine 15 $\mu\text{g}/\text{kg}$	4.0	[2.8, 6.0]	<0.0001	<0.0001
Neostigmine 25 $\mu\text{g}/\text{kg}$	3.2	[1.7, 6.2]	<0.0001	<0.0001
Neostigmine 40 $\mu\text{g}/\text{kg}$	2.0	[1.7, 4.2]	<0.0001	<0.0001

\* Log Rank Test with Sidak adjustment

Source: Reviewer

Based on his analysis of data provided in Schaller et al, he found that neostigmine reduces the recovery time required to reach ToF ratio  $\geq 0.9$  when administered at a ToF ratio of 0.5. He therefore concluded that there is evidence to support the use of neostigmine to reverse neuromuscular blocks.

Since the usual practice of administering reversal is to administer the neostigmine sooner than when ToF is 0.5, but rather when it is closer to a ToF of 0.1, I would not recommend using doses as low as 5 or 8 mcg/kg unless dictated by clinical circumstances (e.g., the patient has spontaneously reversed to a degree of ToF greater than 0.5)

### 3.5.2.1.2.2. Subpopulations

#### Race

The patients' racial identification was rarely reported; efficacy was not analyzed based on this parameter. Based on neostigmine's mechanism of action and its widespread use on patients of both genders and various racial backgrounds, there is no evidence to suggest that its efficacy would be affected by either of these demographics.

#### Age (Elderly)

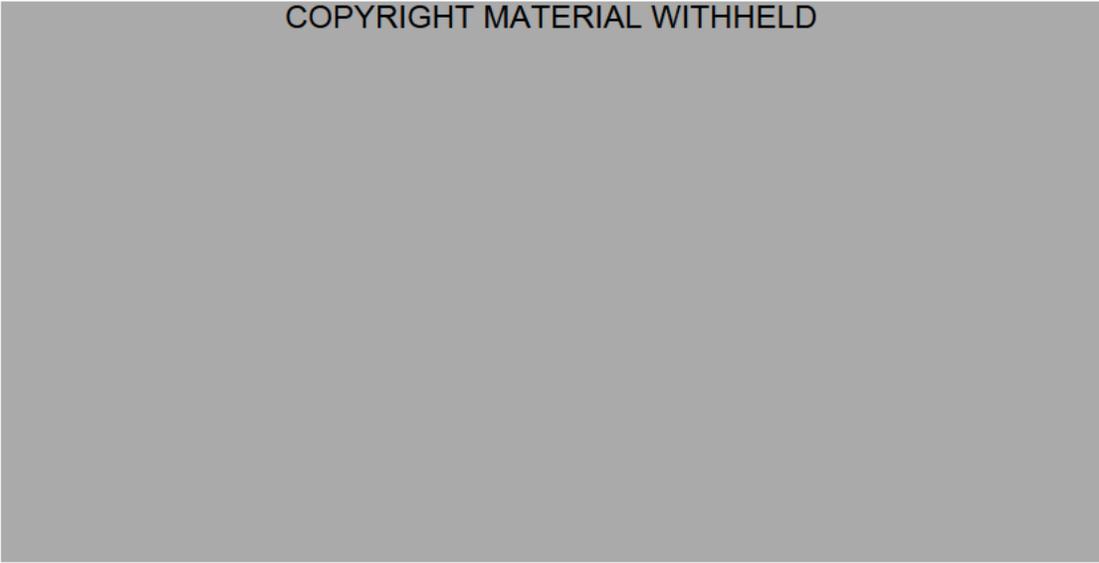
Of the studies cited by Dr. Simone regarding the use of neostigmine in the geriatric population, McCarthy et al. seemed to most systematically examine the dose-response relationship for neostigmine in the elderly.

In this study, neostigmine doses included 5, 15, 25, 35, and 45 mcg/kg. The ToF values at 1-minute intervals from 5 minutes post-study drug administration onwards were used to determine the dose-response relationships. The difference in the time to spontaneous recovery of T1 to 10% between the two treatment groups was significant: 24 minutes (SD = 6) and 33 minutes (SD = 8) for the younger and older

adults, respectively. The dose-response curves for neostigmine reported by the authors are shown in **Figure 2**. While the responses were parallel for the two age groups, those for the elderly were significantly shifted to the right of the curves for the adults, suggesting either a lesser relative potency or an increased dosing requirement of neostigmine by the elderly for antagonizing the neuromuscular blocking effects of vecuronium. Furthermore, the ToF ratios for the two treatment groups showed that increasing doses of neostigmine were associated with faster recovery in both adult and elderly groups; however, the ToF ratios were generally greater and the recovery apparently faster, according to the authors, with every dose of neostigmine in adults compared with the elderly. They further note that doses of neostigmine 25 mcg/kg or less did not achieve satisfactory antagonism by 10 min from this intensity of block, particularly in the elderly.

**Figure 2 Dose-response curves for ToF ratios at 10 min after administration of neostigmine in adults and the elderly.**

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In summary, the results of this study indicated that the efficacy of neostigmine in the elderly, i.e., patients over the age of 70 years, is less than that in younger adults, at least for the first 10 minutes following administration and suggests that the elderly may require about twice the dose of neostigmine to achieve the same ToF ratio as younger adults at 10 minutes.

#### Age (Pediatrics)

Dr. Simone analyzed and summarized (see **Table 7**) the unintegrated literature provided by the Sponsor. In general the data suggest the following:

- Neostigmine seems to be similarly effective in the reversal of neuromuscular blockade of non-depolarizing neuromuscular blocking agents as it is in adults;
- The effect of the dose range (~20-70 mcg/kg) seems similar to that observed in adults. Doses as low as 10 mcg/kg may be effective in certain circumstances (see the following bullet)

- Similar considerations for dose selection within the recommended dose range seem to apply for pediatric patients as in adults (e.g., lower doses with short-acting non-depolarizing neuromuscular blocking agents or when the patient has spontaneously recovered to a greater extent than a single twitch on the ToF);
- There seems to be an increasing effect with increasing dose up to the highest doses tested (~70 mcg/kg).
- Excessive dosing of neostigmine (e.g., high doses in the setting of almost complete reversal of blockade before administration) may result in a paradoxical weakness

The data presented by the Sponsor spans the age range of 0-16 years old. There were notably fewer studies involving those in the youngest part of this population (i.e., <3 mo). However, Dr. Simone and I concur that there does not seem to be any notable deviation of the effects of neostigmine in this age group. Dr. Simone also notes throughout his review that the reversal of NMBAs involves not only the use of neostigmine but also requires a rigorous paradigm of clinical evaluation that should be more than adequate to account for any individual variability in the response to administration of neostigmine according to the proposed labeling.

**Table 7 Summary of Efficacy Data for Neostigmine in Pediatric patients**

NMBA	Dose of Neostigmine (mcg/kg)	Number of Patients	Age Range (years)	When Administered	Efficacy Endpoints	Comments
Vecuronium (VCB)	31	24	2y - 8y	T <sub>1</sub> had 1-25% recovery	Various TOF	Source: Meistelman et al. (58) TOF > 0.9 occurred at 10 min when neostigmine was given at T <sub>1</sub> ≥ 0.1.
	70	40	2y - 6y	Spontaneous; 5 min after VCB; and T <sub>1</sub> had 1-25% recovery	Various TOF	Source: Bevan et al. (41) Glycopyrrolate – 0.01 mg/kg TOF > 0.9 occurred at 30 min when neostigmine was given at T <sub>1</sub> ≥ 0.1.
	30	8 10	3m – 10m 3y – 10y	T <sub>1</sub> = 0.1	Various TOF	Source: Debaene et al. (71) Atropine – 0.1 mg/kg TOF ≥ 0.9 occurred by 15 min.
Mivacurium	5 10 20 50	6 6 6 6	2y – 12y	T <sub>1</sub> = 0.1	T <sub>1</sub> and TOF	Source: Bevan et al. (64) Atropine - 2, 4, 8 or 20 mcg/kg TOF ≥ 0.75 occurred by 10 min for doses of neostigmine ≥ 10 mcg/kg, which was significantly faster than spontaneous recovery.
NMBA	Dose of Neostigmine (mcg/kg)	Number of Patients	Age Range (years)	When Administered	Efficacy Endpoints	Comments
Atracurium	50 10 50	6 6 6	3y - 9y 1y - 8y 1y - 7y	PTC <sub>1</sub> = 0.1 PTC <sub>1</sub> = 0.1 T <sub>1</sub> = 0.1	TOF <sub>0.5</sub>	Source: Gwinnutt et al. (60) Atropine - 0.02 mg/kg TOF = 0.8 at 14 and 12 min after 50 and 10 mcg/kg neostigmine doses, respectively, at PTC <sub>1</sub> = 0.1 and at 5 min after 50 mcg/kg ginvr at T <sub>1</sub> = 0.1
	50	40	0 - <16y	T <sub>1</sub> = 0.1	T <sub>1</sub> and TOF	Source: Kirkegaard-Nielson et al. (79) Atropine - 0.02 mg/kg <1y recovered fastest with TOF <sub>0.5</sub> at 10 min. ≥2y had TOF <sub>0.5</sub> at 15 min.

NMBA	Dose of Neostigmine (mcg/kg)	Number of Patients	Age Range (years)	When Administered	Efficacy Endpoints	Comments
Rocuronium (RCB)	5 10 20 50	8 8 8 8	2y – 10y	$T_1 = 0.1$	TOF	Source: Abdulatif et al. (63) Atropine - 5-20 mcg/kg TOF <sub>0.5</sub> was < 10 min for the 2 highest doses; slightly > 10 min for the 0.1 dose and not reached by 10 min for the lowest dose of neostigmine.
	70	40	2y – 12y	Spontaneous; 5 min after RCB; and $T_1$ had 1-25% recovery	TOF <sub>0.5</sub>	Source: Bevan et al. (41) Glycopyrrolate - 0.1 mg/kg When neostigmine was administered at $T_1=0.1$ , TOF <sub>0.5</sub> was reached at 20 min.
NMBA	Dose of Neostigmine (mcg/kg)	Number of Patients	Age Range (years)	When Administered	Efficacy Endpoints	Comments
Cis-atricurium						No pediatric information provided
d-Tubocurarine (dTc)	6.25 12.5 25	4 4 4	3 wk – 4 m	Neostigmine was administered during dTc infusion after $T_1$ was constant for 15 minutes. Infusion was continued after neostigmine was administered	Time to 70% of peak antagonism	Source: Fisher et al. (57) Atropine - 5, 10 or 20 mcg/kg for corresponding low to high doses of neostigmine For both age groups, the lower doses of neostigmine required 7-9 min for reversal; for the highest neostigmine dose, reversal required 5 min for both age groups.
	6.25 12.5 25	5 5 5	1y – 8y			
NMBA	Dose of Neostigmine (mcg/kg)	Number of Patients	Age Range (years)	When Administered	Efficacy Endpoints	Comments
Pancuronium						No pediatric information provided

### 3.5.2.1.3. Analysis of Secondary Endpoints(s)

The Applicant provided no analysis of secondary endpoints.

### 3.5.2.1.4. Dose identification/selection and limitations

According to Dr. Simone, the recommended dose range is 40 mcg/kg to 70 mcg/kg. Dr. Simone has noted that doses as low as 10 – 20 mcg/kg have been studied and often are able to reverse NMBAs in a reasonable time period, however these doses are not as predictably effective as those greater than or equal to 40 mcg/kg. Since there seems little downside from a safety perspective in starting at this dose (40 mcg/kg), he recommends it as the lower dose in the recommended range at typical conditions for reversal (e.g., ToF 0.1).

Dr. Simone notes in his review that the data in Error! Reference source not found. indicate that low doses (closer to the lower part of the recommended dose range) of neostigmine are adequate to reverse NMBAs with shorter half-lives, e.g., rocuronium. The data also suggest that lower doses of neostigmine are adequate when more substantial levels of spontaneous recovery have occurred.

Limited data was presented regarding the recovery of pancuronium to a level of ToF recovery greater than 70%. This may be attributed, in part, to it being an older drug that would have been evaluated under the “old” gold standard for measuring reversal, which used a ToF ratio of 70%. Data from one study cited by Dr. Simone seem to indicate that pancuronium behaves differently compared to vecuronium, rocuronium, and atracurium because of its stronger binding to the acetylcholine receptor, which may have the effect of reducing the maximal ToF percent recovery.

Regarding persistence of efficacy, some authors reported that they did not observe “recuritization,” i.e., signs or symptoms of recurring neuromuscular blockade; however, systematic assessments using nerve stimulation were not made. With a half-life estimated to be between 77 and 113 minutes, the effects of neostigmine should outlast those of the NMBAs currently used in clinical practice, with the possible exception of pancuronium, which has a half-life estimated to be between 89 and 161 minutes.

Regardless of the NMBA used, patients should be carefully observed following administration of neostigmine due to limitations in interpreting ToF responses in the clinical setting, with the potential for overestimating the extent of reversal; the interactions of other drug product that can affect the intensity or duration of neuromuscular blockade, e.g., volatile anesthetic agents and some antibiotics; and variations in metabolism of the NMBA and neostigmine that can occur due to a patient’s underlying medical condition and concomitant medications.

### 3.5.2.2. Discussion of primary and secondary reviewers' comments and conclusions regarding Efficacy

The following were Dr. Simone's conclusions regarding the efficacy of neostigmine for the reversal of nondepolarizing NMBAs:

1. The studies presented by the Sponsor also provided the following evidence of efficacy:
  - a. Neostigmine significantly reduced recovery time to ToF 0.9 compared to placebo or spontaneous recovery.
  - b. A dose effect was demonstrated for neostigmine; however, there appears to be an upper limit beyond which additional neostigmine does not hasten the recovery, i.e., the dose-response curve plateaus.
  - c. The extent to which neostigmine shortened recovery times varied due to a number of factors; however, the range appears to be on the order of 10 to 60 minutes, which is clinically relevant for reducing patient exposure to anesthetic medications as well as reducing the duration of mechanical ventilation and presence of an endotracheal tube.
  - d. Neostigmine reduced recovery times for all the nondepolarizing neuromuscular blocking agents assessed, although the extent of its effect was variable and appeared to be influenced by a number of factors:
    - i. Extent of spontaneous recovery at the time of its administration,
    - ii. Concurrent use of volatile anesthetic agents
    - iii. Use of certain concomitant medications, e.g., some antibiotics, magnesium sulfate
2. The recommended dose range is 40 mcg/kg to 70 mcg/kg at typical conditions for reversal (e.g., ToF 0.1).
3. The dose of neostigmine should be determined based on the responses to the ToF stimuli with lower doses administered if more twitches are present and higher doses administered if only T1(of 4) is detected.
4. Recovery times vary depending on the degree of neuromuscular blockade at the time neostigmine is administered, the dose of neostigmine administered, and other factors, e.g., the types of anesthetic agents in use at the time of reversal, the patient's body temperature. Generally, recovery to the point where the ratio of the contractile strength of the fourth twitch to the first twitch, T4/T1, is 90% (ToF 0.9) occurs over a period of about 10 minutes.

The following were observations Dr. Simone made regarding the use of Neostigmine that relate to its efficacy or proper monitoring of the drug's effect:

5. A peripheral nerve stimulator should be used throughout the surgical procedure to monitor the patient's twitch response following NMBA administration in order to:
  - a. determine if sufficient spontaneous recovery from the NMBA has occurred to assure the block is reversible
  - b. estimate the dose of neostigmine required to reverse the block
  - c. monitor the reversal of the block after neostigmine administration
  - d. evaluate the need for additional doses of neostigmine
6. Using ToF stimuli, preferably at the ulnar nerve at the level of the wrist, neostigmine should only be administered if there is a detectable twitch response to the first impulse of the ToF, i.e., if the first twitch, T1, is present.
7. Adequacy of the reversal of the neuromuscular block needs to be based on a clinical assessment of the patient and not ToF responses alone.
8. Patients should be monitored for clinical signs of residual blockade (e.g., difficulty maintaining a patent airway, generalized weakness, inadequate ventilatory effort) following cessation of the anesthetic and extubation. The duration of monitoring should take into account the duration of action of the NMBA used and of neostigmine, which is estimated to be 20–30 minutes.

I concur with most all points of Dr. Simone's review, however, I think the choice of 40 mcg/kg as the lower dose in his recommended range should be lowered to 30 mcg/kg. I base this on the following rationale:

- Some of the 11 studies (e.g., see studies by Lederer and Meistelman in **Table 4**) demonstrate that 30 mcg/kg can reverse NMBAs to an adequate degree (Tof 0.9) in a reasonable time (~10 min.);
- The only result that would suggest 30 mcg/kg is not adequate administered neostigmine when the ToF was supposedly at 1% (verses the usual time of ToF 0.1 or 10%) (e.g., see study by Meistelman in **Table 4**). This condition would according to Dr. Simone's other recommendations lead one to use a higher dose of neostigmine (e.g., closer to 70 mcg/kg);
- We have recommended a rigorous paradigm of ToF and Clinical testing to determine whether a dose was adequate for reversal, so if 30 mcg/kg was insufficient, guidance was provided for further treatment or evaluation.

With respect to other aspects of his recommendations, I believe he has adequately discussed the rationale for selecting doses at different points in this range (c.f., Bullets 1c, 1d, 3, and 4 in this section). He has also made an adequate case for using the same dose range for pediatric patients. Consistent with clinical practice, he has stated that specific recommendations for clinical monitoring be included in the labeling. While it could be argued that this breaches into the practice of medicine, I agree with his position because the proper use of the drug is critically dependent on utilizing the monitoring he suggests and despite the literature having been in existence for a long

time, it has not been critically reviewed and succinctly summarized in the manner needed.

### 3.5.3. Safety

#### 3.5.3.1. Background on safety issues with related drugs

As Dr. Simone has noted, the edrophonium and pyridostigmine product labels present safety issues germane to neostigmine including:

1. cardiac arrhythmias, particularly bradycardia,
2. muscarine-like symptoms (nausea, vomiting, diarrhea, sweating, increased bronchial and salivary secretions and bradycardia) often appear with overdosage (cholinergic crisis),
3. increased bronchial secretions,
4. intestinal and urinary obstructions of mechanical type
5. exacerbation of asthma in patients with bronchial asthmatic
6. the need prior or simultaneous injection of atropine sulfate or an equipotent dose of glycopyrrolate to block muscarinic effects
7. adequate recovery of voluntary respiration and neuromuscular transmission prior to discontinuation of respiratory assistance, and even then should be continuous patient observation. Satisfactory recovery may be judged by adequacy of skeletal muscle tone, respiratory measurements, and by observation of the response to peripheral nerve stimulation. A patent airway should be maintained and manual or mechanical ventilation should be continued until complete recovery of normal respiration is assured.

I concur with Dr. Simone's assertion that as an anticholinergic drug, neostigmine has been associated with similar safety issues, and these need to be incorporated into the product's labeling.

#### 3.5.3.2. Review Strategy - Safety

The evaluation of safety was based on both the findings in the submitted literature and a review of the data in the Agency's Adverse Event Reporting System (AERS). All of the literature submitted by the Applicant was reviewed for safety considerations. However, the data derived from placebo-controlled and edrophonium-or pyridostigmine-controlled studies were weighed most heavily in Dr. Simone's characterization of the risk profile as they allowed a comparison in incidence rates. The AERS database was reviewed by the Division of Pharmacovigilance II (DPVII) in the Office of Surveillance and Epidemiology.

The Applicant did not group or categorize adverse events. As the events were reported in the literature and the original data were not retrieved, the Applicant reported the events as described in the publications. No analyses of adverse events

were performed by the Applicant, including summaries or incidence rates of the adverse events reported in the literature. No attempt was made by the Applicant to pool data across studies or to estimate and compare incidence of adverse events. While such an analysis may be possible, Dr. Simone asserted in his review that the results would likely be difficult, if not impossible, to interpret due to the number of confounding factors affecting safety both within and among the studies, e.g., anesthetic agents, surgical procedures, patient demographics, concomitant medical conditions and medications, and coadministration of anticholinergic agents with the neostigmine.

### 3.5.3.3. General safety considerations

#### 3.5.3.3.1. Exposure - Adults

Twenty six (26) articles were identified by the Applicant as providing clinical safety information. These articles provided a database of 1,747 adult patients who were exposed to neostigmine in doses ranging from 10 mcg/kg to 80 mcg/kg. This population included a substantial numbers of both male and female patients as well as geriatric patients. Race of the patients was rarely reported. Table 8 lists the doses and number of subjects used in those twenty-six studies used for the evaluation of safety and the primary safety outcomes measured.

**Table 8 Applicant’s summary of neostigmine clinical safety studies in adults (Table 2.7.4-1 from the NDA)**

Citation	Number of Patients Exposed	Primary Safety Outcome Measured	Dose of neostigmine (mg) or (mg/kg)	Dose of Atropine or Glycopyrrolate (mg or µg/kg)	Agent(s) Reversed
OSTHEIMER ET AL., (1977)(1)	305	Safety assessment between atropine and glycopyrrolate	2.5 mg	atropine (1.0 mg) glycopyrrolate (0.5 mg)	d-tubocurarine or pancuronium
MIRAKHUR ET AL., (1977)(2)	40	Safety assessment between atropine and glycopyrrolate	2.5 mg	atropine (1.2 mg) glycopyrrolate (0.5 mg)	tubocurarine or pancuronium
BROCK-UTNE ET AL., (1978)(82)	20	Lower esophageal tone	2.5 mg 5.0 mg	glycopyrrolate (0.6 mg)	suxamethonium
SALEM ET AL., (1986)(7)	115	Postoperative heart rate and oral secretions	5 mg	atropine (1.2 or 1.8 mg); glycopyrrolate (0.6 mg or 0.9 mg)	pancuronium

Citation	Number of Patients Exposed	Primary Safety Outcome Measured	Dose of neostigmine (mg) or (mg/kg)	Dose of Atropine or Glycopyrrolate (mg or µg/kg)	Agent(s) Reversed
KING ET AL., (1988)(10)	19	Incidence of postoperative nausea and vomiting	2.5 mg	atropine (1.2 mg)	tubocurarine
GOLDHILL ET AL., (1988)(11)	51	Incidence of dysrhythmias, abnormal heart rate and BP	0.01 – 0.08 mg/kg	glycopyrrolate (0.2 mg)	pancuronium
JOHNSON ET AL., (1989)(12)	26	ECG, and arterial pressure	0.01 – 0.04 mg/kg	atropine (0.4 mg/1.0 mg neostigmine)	vecuronium
NAGIUB ET AL., (1989)(13)	70	Change in heart rate via ECG	0.04 – 0.06 mg/kg	atropine (0.014-0.04 mg/kg)	pancuronium
WETTERSLEV ET AL., (1991)(65)	55	Change in heart rate via ECG	0.035 mg/kg	atropine (8.0 µg/kg) glycopyrrolate (7.0 µg/kg)	gallamine
SURSESH ET AL., (1991)(18)	32	Dose response to cardiovascular changes	0.015 – 0.075 mg/kg	glycopyrrolate (3.0-15.0 µg/kg)	atracurium
VANDENBROE K ET AL., (1994)(66)	40	Cardiovascular safety and rate of recovery from neuromuscular block	0.04 mg/kg	methyl-atropine (7.0µg/kg)	rocuronium
BOEKE ET AL., (1994)(23)	40	Incidence of postoperative nausea and vomiting	1.5 mg	atropine (0.5mg)	vecuronium
HARPER ET AL., (1994)(24)	57	Monitoring of vital signs, ECG, capnography and pulse oximetry	0.02 – 0.08 mg/kg	atropine (0.4mg/1mg neostigmine)	atracurium

Citation	Number of Patients Exposed	Primary Safety Outcome Measured	Dose of neostigmine (mg) or (mg/kg)	Dose of Atropine or Glycopyrrolate (mg or µg/kg)	Agent(s) Reversed
CALDWELL ET AL., (1995)(27)	60	Monitoring of ECG and non-invasive MAP	0.02 – 0.04 mg/kg	glycopyrrolate (4.0 or 8.0µg/kg)	vecuronium
DHONNEUR ET AL., (1996)(30)	80	Effect of renal failure on reversal from neuromuscular block	0.04 mg/kg	atropine (20µg/kg)	vecuronium
HOVORKA ET AL., (1997)(32)	80	Incidence of postoperative nausea and vomiting	2.0 mg	glycopyrrolate (0.4mg)	mivacurium
LESSARD ET AL., (1997)(33)	70	Monitoring of ECG, pulse oximetry and non-invasive MAP	0.010 – 0.04 mg/kg	glycopyrrolate (0.25, 0.5, or 1.0mg)	mivacurium
FUCHS-BUDER ET AL., (1999)(34)	24	Incidence of bradycardia	0.02 mg/kg	atropine (10µg/kg)	vecuronium
JOSHI ET AL., (1999)(36)	40	Incidence of postoperative nausea and vomiting	2.5 mg	glycopyrrolate (0.5mg)	mivacurium or rocuronium
MCCOURT ET AL., (1999)(37)	36	Monitoring of ECG, pulse oximetry and non-invasive MAP	0.05 mg/kg	glycopyrrolate (10µg/kg)	rapacuronium with and without rocuronium
MCCOURT ET AL., (1999)(38)	110	Incidence of emetic symptoms	0.02 – 0.05 mg/kg	glycopyrrolate (10µg/kg); atropine (20µg/kg)	rocuronium
PURDY ET AL., (1999)(40)	117	Postanesthetic AEs and SAEs	0.05 – 0.07 mg/kg	glycopyrrolate (0.01mg/kg)	rapacuronium

Citation	Number of Patients Exposed	Primary Safety Outcome Measured	Dose of neostigmine (mg) or (mg/kg)	Dose of Atropine or Glycopyrrolate (mg or µg/kg)	Agent(s) Reversed
BEVAN ET AL., (1999)(41)	80	Monitoring of ECG, pulse oximetry and non-invasive MAP	0.07 mg/kg	glycopyrrolate 0.01mg/kg; atropine (0.02 mg/kg)	rocuronium or vecuronium
HAYES ET AL., (2000)(43)	15	Monitoring of ECG, pulse oximetry and non-invasive MAP	0.05 mg/kg	Not reported	rapacuronium
LARIJANI ET AL., (2001)(44)	119	Heart rate and incidence of bronchospasm	0.05 mg/kg	glycopyrrolate (10mcg/kg)	rapacuronium
TRIBUDDHAR AT ET AL., (2008)(46)	46	Role of different doses of atropine on cardiovascular effects	2.5 mg	atropine (0.9 or 1.2 mg)	vecuronium

### 3.5.3.3.2. Special Populations

#### 3.5.3.3.2.1. Pediatrics

The NDA listed three studies in which clinical safety was assessed in a total of 56 pediatric patients.

**Table 9 Applicant’s summary of neostigmine clinical safety studies in Pediatrics**

Citation	Number of Patients Exposed	Primary Safety Outcome Measured	Dose of neostigmine (mg) or (mg/kg)	Dose of Atropine or Glycopyrrolate (mg or µg/kg)	Agent Reversed
SALEM ET AL., (1977)(56)	20	Hemodynamic response to atropine-neostigmine antagonism of neuromuscular block	0.05 mg/kg	atropine (20 µg/kg)	tubocurarine
DEBAENE ET AL. (1989)(71)	18	Monitoring of ECG, pulse oximetry and non-invasive MAP	0.03 mg/kg	atropine (10 µg/kg)	vecuronium
GWINNUTT ET AL., (1991)(60)	18	Monitoring of ECG, pulse oximetry and non-invasive MAP	0.05 – 0.10 mg/kg	atropine (20 µg/kg)	atracurium

### 3.5.3.3.3. Safety findings from submitted clinical trials

#### 3.5.3.3.3.1. Deaths

The Applicant reviewed historical reports in the literature dating back to 1949 and identified 3 reports of acute cardiac arrest and death in anaesthetized patients following the rapid intravenous administration of neostigmine (**Table 10**). The etiologies of these deaths were attributed to the rapid administration of neostigmine leading to bradycardia or inappropriate timing of administration of an anticholinergic agent (atropine).

**Table 10 Deaths attributed to neostigmine identified in the literature**

Author (Year) Reference	Age	Sex	Neostigmine Dose (mg)	Diagnosis	Cause of Death	Other Medications	Other Medical Conditions
Clutton-Brock (1949) (84)	62 years	Female	2.0 mg	Common bile duct obstruction	Cardiac arrest	Atropine (0.65mg)	Intra-operative cardiac "irregularities"
Hill (1949) (85)	7 months	Not reported	0.25 mg	Congenital atresia of the bile duct	Cardiac arrest	Atropine (0.22 mg)	Autopsy findings normal with exception of bile duct
Macintosh (1949) (86)	38 years	Male	2.5 mg	Acute surgical abdomen	Cardiac arrest	Atropine (0.65mg)	Cardiac hypertrophy and generalized peritonitis found at autopsy

#### 3.5.3.3.3.2. Nonfatal Serious Adverse Events

Nonfatal serious adverse events were not characterized by the Sponsor

#### 3.5.3.3.3.3. Dropouts and Discontinuations

Dropouts and discontinuations were not characterized by the Sponsor

#### 3.5.3.3.3.4. Common Adverse Events

Based on the literature submitted by the Applicant and the AERS database and literature review performed by DPV-2, the adverse events commonly reported for neostigmine were those related to its anticholinesterase activity and contained in the label for the currently marketed, unapproved product. These adverse events are identical to those proposed by the Applicant for inclusion if the product is approved, include those reported for uses of neostigmine outside the scope of the proposed indication, and are listed below:

- **Neurological:** Dizziness, weakness, convulsions, loss of consciousness, drowsiness, headache, dysarthria, miosis and visual changes
- **Cardiovascular:** Cardiac arrhythmias (including bradycardia, tachycardia, atrioventricular block and nodal rhythm) and [REDACTED] cardiac arrest, syncope and hypotension

- **Respiratory:** Increased oral, pharyngeal and bronchial secretions, dyspnea, respiratory depression, respiratory arrest and bronchospasm
- **Dermatologic:** Diaphoresis, flushing, rash and urticaria
- **Gastrointestinal:** Nausea, emesis, flatulence and increased peristalsis
- **Genitourinary:** Urinary frequency
- **Musculoskeletal:** Muscle cramps and spasm, arthralgia

In the only study that reported a detailed list of adverse events for neostigmine and a comparator, Schaller (2010) evaluated the efficacy and safety of neostigmine in doses of 5, 8, 15, 25, or 40 mcg/kg in a mixture with 1 mcg glycopyrrolate/5 mcg neostigmine to sugammadex and saline. The adverse events for all doses of neostigmine were combined for tabular display in the article. **Table 11** lists the findings for the neostigmine and placebo (normal saline) treatment arms of the study.

**Table 11 Adverse Events [n (%)] following neostigmine and placebo treatments**

Adverse Event	Neostigmine (n = 51)	Placebo (n = 9)
Hypertension	1 (2)	0
Bradycardia	12 (27)	0
Hypoglycemia	0	1 (11)
Hypokalemia	1 (2)	1 (11)
Hypocalcemia	1 (2)	1 (11)
Hypotension	3 (7)	4 (44)
Oxygen desaturation < 90%	3 (7)	0
Paresthesia <i>nervus ulnaris</i>	0	1 (11)
Postoperative nausea and vomiting	0	2 (22)
Postoperative shivering	11 (25)	0
Tachycardia	2 (5)	0
Anesthetic complications (intraoperative cough/movement)	1 (2)	0
Acute lung failure (serious AE)*	1 (2)	0
At least 1 AE	28 (64)	4 (44)

\* One patient developed acute lung failure 63 h postoperatively. This AE was categorized as severe and possibly related to the study medication of 5 mcg/kg neostigmine. The patient was known to have a restrictive lung disorder (vital capacity of 1.9 l, i.e., 35% of normal) after bleomycine chemotherapy.

The unexpected finding of Schaller's study was the high incidence of postoperative shivering for neostigmine-treated patients. The authors reported that there were no dose-related responses to any of the adverse events. However, it should be noted that all but one of the neostigmine doses studied were less than 30 mcg/kg, and therefore, this study does not fully characterize its risk profile.

### 3.5.3.3.3.5. Vital Signs

Tachycardia was reported in one publication. Clinically relevant changes in respiratory rate, blood pressure, core body temperature and oxygen saturation were not reported in the literature, according to the Applicant.

### 3.5.3.3.3.6. Electrocardiograms (ECGs)

The Applicant neither summarized nor analyzed the limited ECG information provided in the literature; however they included a list of the safety literature reviewed and the adverse events reported for each article (counts were not provided). As continuous electrocardiographic monitoring is the standard of care in both the operating room and post-anesthesia care unit, and neostigmine-induced rhythm changes are expected to occur within minutes of drug administration, it is likely that the adverse events reported accurately reflect the types of events that occur, if not the incidence for each. The following are the adverse events related to ECG monitoring that were captured by the Applicant from the literature:

1. bradycardia
2. A-V dissociation
3. premature ventricular contraction
4. first degree heart block
5. ventricular extrasystoles
6. cardiac dysrhythmias (not otherwise specified)
7. cardiac arrest (from the list of reports of patient deaths)

#### 2.1.1. Drug-Demographic or –Disease interactions

One study cited by the Applicant compared patients with normal renal function to renal transplant patients and anephric patients. Neostigmine pharmacokinetics were not significantly different in patients with normal renal function from those having undergone renal transplantation; however, anephric patients had a significantly prolonged elimination half-life and decreased total serum clearance of neostigmine when compared to patients with normal renal function or those with recent renal transplantation.

### 3.5.3.3.4. Drug-Drug –Interactions

The Applicant provided the following information regarding drug-drug interactions for neostigmine:

1. Neostigmine should not be used to reverse the effects of depolarizing muscle relaxants such as succinylcholine or decamethonium, as it may prolong the phase-1 block.

2. Certain antibiotics, particularly neomycin, streptomycin and kanamycin have nondepolarizing neuromuscular blocking action and therefore neostigmine dose adjustments may be required to reverse neuromuscular block in patients who have been taking these drugs. Other antibiotics, including tobramycin, gentamicin and cefazolin, have no effect on the nondepolarizing neuromuscular blocking action of d-tubocurarine or its reversal by neostigmine and atropine.

Similarly, there was no effect on the nondepolarizing neuromuscular blocking action of rocuronium by cefuroxime, metronidazole, cefuroxime or metronidazole or its reversal by neostigmine.

However, the literature included in the NDA submission describes several other key interactions that need to be considered in clinical practice and that should be included in product labeling. These are listed below:

1. Neostigmine-induced recovery is attenuated in patients treated with MgSO<sub>4</sub> due to the independent effects of MgSO<sub>4</sub> at the neuromuscular junction rather than a drug-induced decreased response to neostigmine.

2. Volatile anesthetic agents may interfere with neostigmine-induced recovery from neuromuscular blockade if they are not discontinued prior to the administration of neostigmine.

#### 3.5.3.3.5. Immunogenicity, where pertinent

The Applicant provided no information regarding the immunogenicity of neostigmine. None could be found in the literature search performed for this review. There appears to be no evidence suggesting neostigmine is immunogenic despite a history of extensive use of spanning more than five decades, with the possible exception of the case described in **Section 3.5.3.3.6.1.1** on **p. 47** of this review.

#### 3.5.3.3.6. Special safety concerns

##### 3.5.3.3.6.1. Postmarketing Experience

##### 3.5.3.3.6.1.1. Applicant Reported Findings

The Applicant reported that they have an established clinical safety database for neostigmine, and that 7 adverse drug events have been reported to the company since March 2003.

- Three events were considered non-serious;

Of the non-SAEs reported, two involved episodes of hypoventilation following drug administration and one involved an incident of decreased effect with no associated adverse events.

- Four were classified as serious adverse events (SAE).

Two of these SAEs were described by the Applicant as expected based on the product label of neostigmine. One of these involved a patient who experienced a

decreased effect of neostigmine given for neuromuscular blockade reversal during eye surgery. The patient was hospitalized and recovered with no sequelae. The other event involved a patient with an extensive history of hypersensitivity who developed an anaphylactic reaction during an unspecified procedure in which she was administered an anesthetic that included propofol, vecuronium, midazolam, dexamethasone, cefazolin, and, at the end of the procedure, neostigmine to reverse the vecuronium. The patient was hospitalized for two days and recovered with no sequelae. The anesthesiologist suspected vecuronium as the most probable drug causing the event. From my perspective, it is difficult to draw any conclusions regarding the attribution of a causative agent given the number of medications administered and missing details of the case.

The two remaining SAEs were reported in a literature article and were deemed unexpected based on the currently available (unapproved) product label. Both events were cases of non-cardiogenic pulmonary edema (NCPE) that began after administration of a combination of neostigmine and glycopyrrolate, which were used to reverse residual neuromuscular blockade. Further details on these patients and their operative courses may be found in Dr. Simone's review.

#### 3.5.3.3.6.1.2. Division of Pharmacovigilance II Findings – AERS Database

An analysis of the AERS database and literature for adverse events related to the use of neostigmine for the proposed indication was performed by Martin Pollack and colleagues in the Division of Pharmacovigilance II (DPV- 2) in the Office of Surveillance and Epidemiology.

The AERS search was conducted on January 25, 2012, and covered the time period from January 1, 1969 to January 25, 2012. No limitations were imposed on the MedDRA search terms so that all events would be retrieved. The search identified 339 reports, 74 of which were determined to be duplicates. Of the remaining 265 cases, 48 were eliminated for various reasons, e.g., neostigmine had not been given, the event occurred prior to neostigmine administration, illegible report. Neostigmine was used for reversal of neuromuscular blockade in 150 (69%) of the remaining cases, which formed the case series for their analysis. Dr. Pollock noted that Neostigmine was used for NMB reversal in most (69%) cases, followed by various other indications (22%; most common: GI tract stimulation); this information was not reported in the remaining 9% of the cases. The most common reactions were cardiac and respiratory events such as cardiac arrest and respiratory depression which are known events consistent with the cholinergic activity of neostigmine. His analysis of all events reported in this case series, including fatalities, did not identify any new safety issue, for which the proposed label can be strengthened or new events could be added. There were 34 deaths reported in this case series, all of which were not directly related to neostigmine. Given that neostigmine is commonly administered in a

setting of surgery along with many other medications, attribution to neostigmine could not be established in many of the AERS cases by the OSE team.

The adverse events of the 150 cases are listed by preferred terms below.

**Table 12 Adverse Events from an AERS search on neostigmine that are found in the current unapproved label**

Labeled Adverse Events by Preferred Term	Adverse Event Count
<b>SOC (All)</b>	268
<b>Cardiac SOC (All)</b>	129
Cardio and/or respiratory arrest	27
Bradycardia or decreased heart rate	23
Tachycardia or heart rate increased	19
Arrhythmias (ventricular, atrial, NOS)	18
Hypotension or blood pressure decreased	14
Atrioventricular block	13
EKG abnormal	10
Myocardial infarction	2
<b>Resp SOC (All)</b>	74
Oxygen saturation decreased/hypoxia	15
Respiratory arrest, depression, distress or failure	13
Dyspnoea or apnoea	12
Bronchospasm or laryngospasm	7
Respiratory acidosis	4
Cyanosis	3
Hypercapnia	3
Increased bronchial secretion/laryngoedema	3
Stridor or wheezing	3
Cough	2
Hypoventilation	2
Respiration abnormal	2
<b>Nervous SOC All</b>	25
Sedation, somnolence or asthenia	10
Coma or LOC	7
Convulsion	3
<b>GI SOC (All)</b>	9
Nausea or vomiting	4
Abdominal pain/pain	2
Diarrhoea	2
<b>Skin SOC (All)</b>	9
Rash/erythema/urticaria	7
<b>Vascular SOC (All)</b>	7
Shock/circulatory collapse	5
Flushing	2
<b>Immune SOC (All)</b>	5
Anaphylaxis/hypersensitivity	5
<b>Musc SOC (All)</b>	5
Muscle spasms/twitching	4
<b>Eye SOC (All)</b>	4
Miosis/visual changes	4

**Table 13 Adverse event counts for events not described in the current unapproved label**

SOC	Adverse Events (n ≥ 2)
Blood (12)	Lymphocyte abnormalities (2); hemoglobin changes (2); decreased protein parameters (2); coagulation abnormalities (2)
Cardiac (15)	Blood pressure increased (11)
Gastrointestinal (7)	GI hemorrhage (2)
General (61)	Drug ineffective (36); drug interaction (7); pyrexia (3); malignant hyperthermia (3); injection site complication (3); edema (3); multi-organ failure (2)
Hepatobiliary (14)	Hepatic failure or injury (3); hepatitis (3); bilirubin increased (2); cholestasis or cholelithiasis (2); increased LFT (2)
Infection (3)	Sepsis (2)
Injury and poisoning (35)	Post procedural complication (11); delayed recovery from anesthesia or prolonged NM block (9); medication error-related (6); anesthetic complication (4)
Metabolic (7)	Metabolic acidosis (3)
Musculoskeletal (8)	Rhabdomyolysis-related (3)
Nervous (23)	Paralysis or hypotonia (7); unresponsive to stimuli or hypoaesthesia (5); serotonin syndrome (2); dyskinesia (2)
Psychiatric (10)	Anxiety related (6)
Renal (12)	Hematuria (3); oliguria (2); renal infarct or thrombosis (2)
Respiratory (18)	Pulmonary edema (5); breath sounds abnormal (2); bronchial or pulmonary hemorrhage (2)
Skin (7)	Blister or drug eruption (2)

#### 3.5.3.3.6.1.3. Division of Pharmacovigilance II Findings – Literature Search

On March 28, 2012, DPV-2 conducted their literature search using PubMed to identify English-language literature using “neostigmine” in the title and the word “adverse” as an unrestricted search term. Those case reports that had not been submitted to the NDA or to AERS formed the basis for this portion of their review.

**Table 14 OSE Safety Literature Search Strategy**

<b>Table 2.2 Literature Search Strategy</b>	
Date of search	3/28/12
Database	PubMed
Search Terms	In title: “neostigmine” and “adverse”
Years included in search	Unrestricted
Language	English

The search resulted in 52 reports with dates of publication ranging from 1948 through 2011; these included 2 cases in which the patient died. Most of the reports (n=23) concerned patients who received neostigmine to reverse the effects of a nondepolarizing neuromuscular blocking agent after surgery.

Regardless of the indication for use, the adverse events associated with neostigmine administration were either labeled events or consistent with labeled events. These included asystole, bradycardia, atrioventricular block, hypotension, excess salivation, and nausea, abdominal pain, anaphylaxis, and bronchospasm. Other reported adverse events included increased or decreased pharmacological effects attributed to renal failure (5 patients), hypokalemia, and concomitant use of medications (beta blockers (4), verapamil (1), methyldopa (1), or reduced or atypical cholinesterase activity (4).

There was case of anaphylaxis (a labeled event) in which the role of neostigmine was supported by a skin prick test. One of the cardiovascular adverse event reports was of a fetus who experienced a drop in heart rate, with no other adverse event, following administration of neostigmine to the mother.

There were five deaths that were included in the review, two of which involved the proposed indicated use. The first was reported by Middleton et al. (1957)(92) and involved a patient who died from cardiovascular shock 23 hours after reversal of apnea with neostigmine during surgery for an abdominal gunshot wound. The authors attributed the apnea to neomycin rather than neuromuscular blockade and did not attribute the death to neostigmine. The second death was reported by Buzello et al. (1982)(93) and involved a 57 year-old woman with dystrophia myotonica who died of bronchopneumonia, hypoxemia, hypercapnia, and recurrent bradyarrhythmia approximately 3 weeks after neostigmine had been given for reversal of pancuronium following a cholecystectomy.

The DPV-2 reviewers concluded that the neostigmine associated adverse events reported in the literature, both related to the proposed indication and otherwise, primarily involved labeled events and deaths due to various causes that appeared to be unrelated to neostigmine. The review of these adverse events, including the deaths, did not reveal any safety concerns not already addressed in the proposed label.

No safety risks were identified from AERS and literature that merit changing the proposed neostigmine label.

#### 3.5.3.4. Discussion of primary reviewer's comments and conclusions

Dr. Simone's principle determination with respect to the safety of the drug for the intended indication is that the risks of neostigmine have been well characterized by the applicant, are mostly consistent with the drug's mechanism of action, and can be readily monitored and treated in the perioperative setting.

The OSE/DPV2 review of adverse events, including the deaths, did not reveal any safety concerns not already addressed in the proposed label.

I concur with both reviewer's recommendations.

## 4. Advisory Committee

No advisory committee meeting was convened to discuss this application. An advisory committee meeting was not deemed necessary to judge whether the data were adequate to establish the efficacy or safety of neostigmine methylsulfate injection for the indication of reversal of non-depolarizing neuromuscular blocking agents.

## 5. Pediatrics

The Division made a case to the PeRC that the NDA contained sufficient information for pediatric labeling and that further studies would not likely result in a further refinement of the dosing guidance or additional safety findings. This was based on the following rationale:

### Pediatric efficacy (see also Section 3.5.2.1.2.2)

The efficacy studies were similar in design to the studies conducted in adult patients and had similar limitations for deriving a uniform method of using neostigmine to reverse the effects of NMBAs. Nonetheless, the findings for pediatric patients were similar to those for adults as they relate to when the drug should be given relative to the extent of spontaneous recovery, the range of dosing (by body weight) that should be administered, and the recovery times of the ToF ratios. The data indicate that neostigmine is equally efficacious across pediatric age groups when adult dosing paradigms are applied. Furthermore, the efficacy results were similar for the NMBAs more commonly used in the pediatric patient population.

### Pediatric pharmacokinetics (see also Section 3.3.2.3)

The available pharmacokinetic data, summarized in the last table below, indicate that PK parameters are similar across pediatric age groups and are also similar to those measured in adults.

### Pediatric safety (see Section 3.5.3.3.2.1)

The safety findings reported in the published literature were limited and were supplemented by a review of available safety data in the literature and the AERS database by conducted by the Division of Pharmacovigilance 2. There were three key findings:

1. The reported adverse events for pediatric patients were similar to those observed in the adult population and were neither severe nor life-threatening.
2. No unexpected adverse events occurred in pediatric patients that raised a safety concern.
3. The use of anticholinergic agents (atropine and glycopyrrolate) counteracted the well-known and predictable effects of neostigmine at the sites of muscarinic cholinergic transmission occurring in the parasympathetic, postganglionic receptors of the autonomic nervous system (most notably bradycardia and bronchoconstriction). The timing of administration and dosing (by weight) of these agents in pediatric patients was the same as for adults;

In light of this data, the Division had the following summary findings upon which it derived its recommendation to the PeRC:

- The evidence supporting the use of 30 to 70 mcg/kg in the pediatric population is adequate. Dosing in the youngest group (0 to 3 months) seems to be similar to that of older pediatric age groups and adults.
- Given the influence of confounding factors (different PK of different NMBAs, different concomitant adjunctive medications used in anesthesia), further studies of dosing for neostigmine in the pediatric population are not likely to result in a more refined dosing guidance than that which is proposed by the Sponsor.
- Given the extensive monitoring of patients after neostigmine administration, which is detailed in the proposed labeling, further study in the pediatric population is not likely to result in the description of a safer paradigm of clinical use of neostigmine.

The PeRC agreed with the Division's position without further comment and requested a copy of the final pediatric labeling be sent to them.

## 6. Other Relevant Regulatory Issues

### 6.1. *Financial Disclosure*

Not applicable. No new clinical trial data were reviewed for this application.

## 7. Labeling

### 7.1. *Physician labeling*

At this time, the review of the Applicant's proposed product labeling is ongoing.

## 8. DSI Audits

During the 6/13 – 7/8/11 inspection of the APP manufacturing facility located at 3159 Staley Road, Grand Island, New York, 14072-2028, investigator(s) from the Food and Drug Administration (FDA) New York District identified the following:

- Significant violations of Current Good Manufacturing Practice (CGMP) regulations for Finished Pharmaceuticals according to [21 U.S.C. § 351(a)(2)(B)].
- Violation of 21 U.S.C. §§ 331(d) and 355(a) for manufacturing prescription drugs without an approved application
- Failure to submit NDA Field Alert Reports (FARs) to FDA in compliance with 21 C.F.R. § 314.81 (b)(l)(ii), as required by section 505(k) of the Act [21 U.S.C. § 355(k)].

The firm supplied a response of 07/29/11, but it was determined by the Agency to lack sufficient corrective actions. A Warning Letter (NYK-2012-14) was sent to the Sponsor 2/22/2012.

The recommendation from the Office of Compliance for this NDA remains as “withhold”. The manufacturing site was supposed to have been reinspected by late December but at the time of this review, it has not taken place<sup>3</sup>.

## 9. Conclusions and Recommendations

### 9.1. *Recommended regulatory action*

I recommend Approval pending satisfactory resolution of the inspection issues (see **Section 3.1.2**).

#### 9.1.1. Risk:Benefit Assessment

While pharmacological reversal of NMBAs, with a drug such as Neostigmine, is not absolutely mandatory in the conduct of an anesthetic case, Dr. Simone has outlined (see **Section 2.1**) a number of reasons why it is not only desirable but may also enhance patient safety.

As this product has been marketed for decades within the United States without identification of significant risks and given its acute use as a single dose per procedure in most all cases, I believe it has a favorable risk:benefit profile.

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<sup>3</sup> Personal communication with Dr. Peri Prasad on 12/28/12

9.2. ***Safety concerns to be followed postmarketing***

9.2.1. Risk Minimization Action Plan, if any

I do not feel a plan beyond routine post-marketing pharmacovigilance is required for this approval given its known safety profile, long history of use, and well established practices of monitoring for reversal of NMBAs.

9.2.2. Postmarketing studies, voluntary or required

Postmarketing studies have been requested by the Nonclinical Team. These are described in **Section** Error! Reference source not found.

9.3. ***Comments to be conveyed to the applicant in the regulatory action letter***

None.

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/s/  
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CHRISTOPHER D BREDER  
01/06/2013