

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203629Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 203629	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Established/Proper Name: Neostigmine Methylsulfate Dosage Form: Injection Strengths: 0.5 mg/mL and 1.0 mg/mL		
Applicant: Fresenius Kabi		
Date of Receipt: 12/29/11; RS 7/11/14		
PDUFA Goal Date: CR 1/29/13; 1/9/15		Action Goal Date (if different): 1/8/15
Proposed Indication(s): indicated for reversal of non-depolarizing neuromuscular blocking agents		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
NDA 000654 Prostigmine	Historical Document, DESI designated NDA
(b) (4)	
Published literature	

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

A waiver of in vivo BA/BE studies was requested for the proposed product based on the following relationships with the referenced literature products: (1) Products are administered intravenously; (2) Products include the same active moiety; (3) Products have the same or similar inactive ingredient composition. Any observed differences in inactive ingredient composition were not known to affect bioavailability; (4) Products have the same intended use.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If “NO,” proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

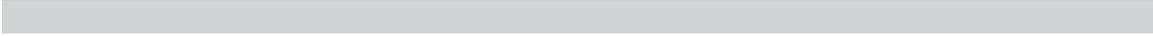
If “NO,” proceed to question #5.

If “YES”, list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

N/A NO YES

APPEARS THIS WAY ON ORIGINAL



RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process: NDA 000654

- c) Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "NO" to (a) proceed to question #11.

If "YES" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES NO

If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES NO

If “**YES**” and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If “**NO**” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS
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- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed proceed to question #14

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If “**NO**”, list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the

application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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/s/

ALLISON MEYER
01/08/2015

PARINDA JANI
01/08/2015

The drug product is currently a marketed unapproved drug. Prior clinical experience does not fully address the safety of potential leachables from the container closure system. Given the long clinical experience with this drug, and based on preliminary data suggesting safety, this study was deemed acceptable as a post-marketing requirement.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Although the rubber stopper that is part of the container closure system has been used in many FDA-approved drug products, this intravenous formulation contains phenol, which may alter the leachable profile. There are at least two ANDA products that have used this stopper for phenol containing drug products; however, an adequate extractable leachable study was not conducted at that time. This study will be completed to assess the safety of the container closure based on current practices.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)?
If the study or trial will be performed in a subpopulation, list here.

The study is an extractable/leachable study to more fully characterize the container closure system.

Required

- Observational pharmacoepidemiologic study
 Registry studies
 Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 Pharmacokinetic studies or clinical trials
 Drug interaction or bioavailability studies or clinical trials
 Dosing trials
 Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 Immunogenicity as a marker of safety
 Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 Dose-response study or clinical trial performed for effectiveness
 Nonclinical study, not safety-related (specify)

- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 Are the objectives clear from the description of the PMR/PMC?
 Has the applicant adequately justified the choice of schedule milestone dates?

- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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/s/

ALLISON MEYER
01/08/2015

JUDITH A RACOOSIN
01/08/2015

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: January 2, 2015

Requesting Office or Division: Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Application Type and Number: NDA 203629

Product Name and Strength: Neostigmine Methylsulfate injection 0.5 mg/mL and 1 mg/mL

Submission Date: December 22, 2014

Applicant/Sponsor Name: Fresenius Kabi USA, LLC

OSE RCM #: 2014-2216

DMEPA Primary Reviewer: Millie Brahmhatt, PharmD, BCPS

DMEPA Acting Team Leader: Vicky Borders-Hemphill, PharmD

1 PURPOSE OF MEMO

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that we review the revised container label and carton labeling (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹ One recommendation that we made was to revise the NDC numbers so that the container label and carton labeling have different NDC numbers to convey the difference in package size between a single vial and 10 vials per carton package configurations. Fresenius Kabi USA, LLC did not implement this recommendation with this submission; and responded “FK USA’s NDC numbering system impacts hundreds of products and several internal systems, standard operating procedures, and departments. Therefore, there are several constraints preventing FK

¹ Brahmhatt M. Label and Labeling Review for Neostigmine methylsulfate injection (NDA 203629). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 DEC 16. 19 p. OSE RCM No.: 2014-2216.

USA from revising the NDC numbers listed on the proposed Neostigmine labels at this time. We are committed to work through the issues and are hopeful to resolve the issue so that we can revise the NDC numbers per your request. At this time, the work is ongoing but we cannot provide the new NDC numbers in this submission.” We do not have any objection to the Applicants NDC proposal.

Additionally, we had recommended including the strength in the same color block as the total drug content per total volume, which was not implemented and rationale was not provided. All other recommended revisions were made.

2 CONCLUSIONS

The revised container label and carton labeling are acceptable from a medication error perspective.

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/s/

MILLIE C BRAHMBHATT
01/02/2015

BRENDA V BORDERS-HEMPHILL
01/02/2015

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: December 31, 2014

To: Allison Meyer, Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products

From: Jessica Fox, PharmD, RAC, Regulatory Review Officer
Office of Prescription Drug Promotion

Subject: NDA 203629
NEOSTIGMINE METHYLSULFATE injection, for intravenous use

As requested in the Division of Anesthesia, Analgesia, and Addiction Products' (DAAAP) consult dated December 19, 2014, the Office of Prescription Drug Promotion (OPDP) has reviewed the NEOSTIGMINE METHYLSULFATE prescribing information.

OPDP's comments on the prescribing information are provided directly below in the proposed version of the labeling obtained at [\\Fdfs01\ode2\DAAAP\NDA and sNDA\NDA 203629 \(Neostigmine APP\)\Labeling\2nd cycle](#) on December 31, 2014.

Thank you for your consult. OPDP appreciates the opportunity to provide comments. If you have any questions, please contact Jessica Fox at (301) 796-5329 or at Jessica.Fox@fda.hhs.gov.

17 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/

JESSICA M FOX
12/31/2014

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: December 16, 2014
Requesting Office or Division: Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number: NDA 203629
Product Name and Strength: Neostigmine Methylsulfate injection 0.5 mg/mL and 1 mg/mL
Product Type: Single ingredient
Rx or OTC: Rx
Applicant/Sponsor Name: Fresenius Kabi USA, LLC
Submission Date: December 12, 2014
OSE RCM #: 2014-2216
DMEPA Primary Reviewer: Millie Brahmhatt, PharmD, BCPS
DMEPA Team Leader: Vicky Borders-Hemphill, PharmD

1 REASON FOR REVIEW

Fresenius Kabi USA, LLC submitted a labeling amendment for Neostigmine methylsulfate (NDA 203629), a currently marketed unapproved product for the indication of reversal of neuromuscular blockade on August 29, 2014. The Applicant submitted the labeling amendment in response to the Complete Response letter dated January 29, 2013, which included a commitment to provide revised draft labeling. The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that we review the proposed container labels, carton labeling, and prescribing information for Neostigmine methylsulfate injection to determine whether they are acceptable from a medication error perspective.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B
Previous DMEPA Reviews	C
ISMP Newsletters	D
Container Labels and Tray Labeling	E
Highlights of Prescribing and Full Prescribing Information	F

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container label, carton labeling, and prescribing information, to identify deficiencies that may lead to medication errors and areas for improvement. We previously provided label/labeling recommendations in OSE review

2012-239¹ (dated May 25, 2012); however, our recommendations were not implemented since the application received a Complete Response.

Prescribing Information

Our review of the *Dosage and Administration* section in the Highlights of Prescribing and the Full Prescribing Information determined inconsistencies between Bloxiverz (neostigmine methylsulfate injection), which is the FDA-approved Neostigmine methylsulfate injection product and the proposed product. We recommend the *Dosage and Administration* section of the proposed Neostigmine methylsulfate injection product be consistent with the FDA-approved product, Bloxiverz, in order to mitigate the risk for confusion and medication errors. Additionally, we identified trailing zeros, error-prone abbreviations and symbols, missing units of measure following numbers used to express dose, undefined abbreviations, and missing space between dose and unit of measure. Furthermore, we recommend route of administration be stated more clearly. Thus, we make recommendations to mitigate confusion and promote safe use of this product in Section 4.1 and Appendix F.

Container Labels and Tray Labeling

Our review of the container labels and tray labeling identified areas of improvement to increase clarity and prominence of important information. Thus, we provide recommendations to mitigate confusion and promote the safe use of this product in Section 4.2.

FAERS and ISMP Newsletter Search

We conducted a FAERS search to inform our review of the proposed labels and labeling. Our search identified six cases since our last FAERS search in a previous review of Neostigmine methylsulfate. However, none of the six cases retrieved were relevant to this review because they described adverse drug events unrelated to a medication error. Additionally, we searched ISMP newsletters and identified two cases. We excluded both cases because they describe hazardous conditions associated with look-alike labels of other manufacturers of Neostigmine methylsulfate. Thus, we do not have recommendations to address these cases.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase clarity and prominence of important information to promote safe use of this product.

¹ Baugh D. Label, Labeling, and Packing Review for Neostigmine Methylsulfate injection (NDA 203629). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2012 MAY 25. 15 p. OSE RCM No.: 2012-239.

If you have further questions or need clarifications, please contact Lisa Skarupa, OSE Project Manager, at 301-796-2219.

4.1 RECOMMENDATIONS FOR THE DIVISION

We have revised the *Dosage and Administration* and *Dosage Forms and Strength* sections of the Highlights of Prescribing and Full Prescribing Information (See Appendix F) and have provided a detailed summary below for review and consideration by DAAAP.

A. Highlights of Prescribing Information

1. We note inconsistencies in the *Dosage and Administration* section between the FDA-approved product, Bloxiverz (neostigmine methylsulfate injection), and the proposed product. We recommend the *Dosage and Administration* section of the proposed product be consistent with the FDA-approved product, Bloxiverz, in order to mitigate the risk for confusion and medication errors.
2. We note route of administration is not clearly stated in the *Dosage and Administration* section. We recommend adding the route of administration to this section so that it is clear that this product may be administered by the intravenous route.
3. We note units of measure are missing following numbers expressing dose. We recommend adding a unit of measure immediately following all numbers, as appropriate.²
4. We note space is missing between the dose and the unit of measure. We recommend placing adequate space between the dose and unit of measure.³
5. We note the use of the error-prone abbreviation “IV.” We recommend replacing the error-prone abbreviation “IV” with the appropriate full meaning of “intravenous.”³

²Food and Drug Administration. *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, April 2013. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

³ISMP’s List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2013 [cited 2014 November 12]. Available from: <http://www.ismp.org/tools/errorproneabbreviations.pdf>.

6. We note the use of dilution ratios (1:1000 and 1:2000) in the *Dosage Forms and Strengths* section. We recommend deleting dilution ratios as this information is not useful to the end user, is not consistent with how this drug product is dosed (e.g., in milligrams per kilograms of drug), and is not consistent with how the recommended dosing is cited in commonly used drug databases.⁴

B. Full Prescribing Information

1. See A.1 through A.5
2. We note the section (b) (4) is prone to confusion and contains several undefined abbreviations (b) (4). The information contained in this section is inconsistent with the FDA-approved product, Bloxiverz (neostigmine methylsulfate injection). We recommend maintaining consistency between the FDA-approved product and the proposed product in order to mitigate the risk for confusion and medication errors. Additionally, we recommend defining abbreviations the first time they are used.
3. We note the use of the error-prone symbols “<,” “≥,” and “>.” The use of these error-prone symbols is dangerous because they can be mistaken as the opposite of the intended meaning. We recommend replacing the error-prone symbols with the appropriate full meaning of “less than,” “greater than or equal to,” and “great than” respectively.²
4. We note the use of trailing zeros which are error-prone and can result in a ten-fold error of measurement if the decimal point is not seen (for example, “1.0” can be misinterpreted as “10”). We recommend removing trailing zeros where they appear in the Full Prescribing Information.⁴
5. In the *Dosage Forms and Strength* section, we note units of measure are missing following numbers expressing strength. We recommend adding a unit of measure immediately following all numbers, as appropriate.³

⁴ Food and Drug Administration. *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, April 2013. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

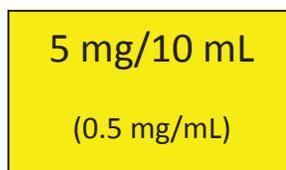
4.2 RECOMMENDATIONS FOR FRESENIUS KABI USA, LLC

We recommend the Applicant implement the following changes prior to approval of this NDA:

A. Container Label (10 mL vial, 0.5 mg/mL and 1 mg/mL)

1. Revise the presentation of the established name from all upper case letters “NEOSTIGMINE METHYLSULFATE INJECTION, USP” to title case “Neostigmine Methylsulfate Injection, USP” to improve readability. We recommend using title case because words written in all capital letters are less legible than words written in title case.⁵
2. Revise the NDC numbers so that the container label and carton labeling have different NDC numbers to convey the difference in package size between a single vial and 10 vials per carton package configurations.⁵
3. Revise the font size of the total drug content relative to the concentration in accordance with USP General Chapter <1> requirements. The total drug content should be more prominent. Additionally, include the total drug content and the concentration within the same color block. For example,

Neostigmine Methylsulfate Injection, USP



4. Ensure the product barcode is added to each individual container label as required per 21 CFR 201.25(c)(2).
5. Relocate the “Rx only” statement to the bottom right side of the principal display panel to ensure there is adequate space for more important information.
6. Delete the extraneous numbers (e.g., “38210” and “38310”) located to the right of the NDC number at the top of the principal display panel to avoid confusion.

B. Tray Labeling (10 mL vial, 0.5 mg/mL and 1 mg/mL)

1. See A.1 through A.6
2. Combine the net quantity, vial size, and packaging configuration into one statement. For example, "10 Multiple Dose Vials – Each vial contains 10 mL." Use one font size for the entire statement.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Neostigmine Methylsulfate injection that Fresenius Kabi USA, LLC submitted on October 29, 2014.

Table 2. Relevant Product Information for Neostigmine Methylsulfate injection	
Initial Approval Date	N/A
Active Ingredient	neostigmine methylsulfate
Indication	Reversal of nondepolarizing neuromuscular blocking agents
Route of Administration	intravenous
Dosage Form	multiple dose vials
Strength	0.5 mg/mL and 1 mg/mL
Dose and Frequency	(b) (4) mg/kg to 0.07 mg/kg. (b) (4)
How Supplied	10 mL multiple dose vials in packages of 10
Storage	20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]
Container Closure	vial

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

DMEPA previously performed a search of the FDA Adverse Event Reporting System (FAERS), reported in OSE Review # 2013-891⁵ (dated May 13, 2013) to identify medication errors related to use of neostigmine. Therefore, we searched FAERS on November 18, 2014 and limited our search to cases received since the previous review from April 12, 2013 to November 1, 2014. We used the criteria in Table 3, and then individually reviewed each case. We limited our

⁵Lee J. Label and Labeling Review for (b) (4) (Neostigmine Methylsulfate Injection, USP) (NDA 204078). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 MAY 13. 11 p. OSE RCM No.: 2013-891.

analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when the reporter provided sufficient information.⁶

Table 3: FAERS Search Strategy	
Date Range	April 12, 2013 to November 18, 2014
Product	Neostigmine Methylsulfate [active ingredient]
Event List (MedDRA Terms)	DMEPA Official Search Terms

B.2 Results

Our search identified six cases, of which none described errors relevant for this review. Thus, we excluded all six cases because they described adverse drug events unrelated to a medication error.

B.3 List of FAERS Case numbers

Not Applicable.

B.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

⁶ The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L: drive on November 18, 2014 using the term, neostigmine, to identify reviews previously performed by DMEPA.

C.2 Results

Our search identified eight previous reviews, and we confirmed our previous recommendations were implemented or considered.

OSE Review # and Date	Summary
2014-730-1 dated September 30, 2014	We evaluated the revised container labels, carton labeling, and tertiary packaging for Bloxiverz (neostigmine methylsulfate) Injection, USP to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review. We found the revisions acceptable.
2014-730 dated June 23, 2014	We evaluated the proposed addition of tertiary labeling to the outside of the shrink-wrapped package of ten cartons and revisions to the content and placement of the package insert labeling. In addition, we evaluated current labels and labeling against recommendation from OSE review # 2013-891 dated May 13, 2013. We made recommendations to improve the labels and labeling.
2013-1092 dated May 23, 2013	We evaluated the proposed proprietary name Bloxiverz for NDA 204078 and found it acceptable.
2013-891 dated May 13, 2013	We provided label and labeling recommendations from OSE review #2012-1763 that were not implemented. We also conducted a FAERS search date ending April

	12, 2013.
2012-2631 dated May 1, 2013	This is a Proprietary Name Review Memorandum regarding (b) (4) (Neostigmine Methylsulfate) Injection, USP.
2012-1763 dated November 15, 2012	We evaluated proposed labels and labeling for neostigmine methylsulfate injection, USP (NDA 204078) and provided recommendations to increase the readability and prominence of important information.
2012-1762 dated October 25, 2012	We evaluated the proposed proprietary name, (b) (4) from a safety and promotional perspective. We found the proposed proprietary name acceptable.
2012-239 dated May 25, 2012	We evaluated proposed labels and labeling for neostigmine methylsulfate injection, USP (NDA 203629) and provided recommendations to improve readability and increase prominence of important information. Application status is CR since 1/29/2013. These recommendations were not implemented and are included in this review.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

We searched the Institute for Safe Medication Practices (ISMP) newsletters on November 21, 2014 using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care, Community, and Nursing
Search Strategy and Terms	Match Exact Word or Phrase: neostigmine methylsulfate

D.2 Results

Our search identified two cases, of which none described errors relevant to this review. Thus, we excluded both cases because they described hazardous conditions associated with look-alike labels of other manufacturers of Neostigmine methylsulfate.

APPENDIX E. LABELS AND LABELING

E.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,⁷ along with postmarket medication error data, we reviewed the following Neostigmine Methylsulfate injection labels and labeling submitted by Fresenius Kabi USA, LLC on December 12, 2014.

- Container label
- Tray labeling

E.2 Label and Labeling Images



⁷ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

MILLIE C BRAHMBHATT
12/16/2014

BRENDA V BORDERS-HEMPHILL
12/16/2014

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: January 14, 2013

To: Allison Meyer
Regulatory Project Manager
Division Anesthesia, Analgesia, and Addition Products (DAAAP)

From: Eunice Chung-Davies, Pharm.D., Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)

CC: L. Shenee' Toombs, Pharm.D., Regulatory Review Officer
Division of Consumer Drug Promotion (DCDP)

Subject: NDA 203629
DPDP labeling comments for neostigmine methylsulfate

In response to DAAAP's January 8, 2013, consult request, DPDP has reviewed the draft proposed Prescribing Information (PI) for neostigmine methylsulfate.

The version of the PI used in this review was emailed from Allison Meyer, RPM, on January 7, 2013 entitled, "pi numbered1 clean.doc." DPDP's comments on this version are provided directly on the attached marked up copy.

Thank you for the opportunity to comment on this PI.

If you have any questions regarding the comments, please contact Eunice Chung-Davies at 301-796-4006 or eunice.chung-davies@fda.hhs.gov .

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immediately following this page.

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/s/

EUNICE H CHUNG-DAVIES
01/14/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: 7/11/2012

Reviewer(s): Martin Pollock, Pharm. D., Safety Evaluator
James Kaiser, M.D., Medical Officer Team Leader
Division of Pharmacovigilance II (DPV-2)

Team Leader: Lauren Choi, Pharm. D., DPV-2

Deputy Division Director: Bindi Nikhar M.D., DPV-2

Product Name(s): Neostigmine (injection)

Subject: All adverse events

NDA Number: 203629

Applicant/Sponsor: APP Pharmaceuticals

OSE RCM #: 2012-239

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EXECUTIVE SUMMARY

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) has received a literature-based NDA (203629) for neostigmine injection, a currently marketed unapproved product. The sponsor's proposed indication is for reversal of neuromuscular blockade. DAAAP requested a review of AERS¹ and the published literature for postmarketing adverse events associated with neostigmine in order to determine if there is any new information that should be incorporated into the sponsor's proposed neostigmine label.

Our review of AERS data identified 217 reports. 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. Our 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.

We found 52 reports from our literature search.² We found events that were labeled or consistent with what is labeled. This did not reveal any new safety concerns not addressed in the sponsor's proposed label. Reversal of nondepolarizing NM block was the most common indication (n=23); most common other indication was treatment of nonmechanical intestinal obstruction (n=15). There were 7 deaths of various causes. Four occurred days to weeks after neostigmine administration; one occurred nearly a day after completion of abdominal surgery; one occurred during an illness that was postulated to have resulted in an overdose; and one occurred after bradycardia in a patient with myasthenia gravis. Labeled events for proposed indicated use or other indications included cardiac events, (e.g. asystole, bradycardia, hypotension), anaphylaxis, and bronchospasm. In addition, cases were reported of increased or decreased neostigmine effects attributed to renal failure, other drugs, and abnormal cholinesterase activity.

As there were no safety risks identified from AERS and literature that merit changing the proposed neostigmine label, we have no recommendations beyond routine safety monitoring at this time.

¹Adverse Event Reporting System

²For published articles of a patient(s) experiencing an adverse event(s) after receiving neostigmine that the sponsor did not submit to this NDA and or were not present in AERS (for which there were 44 citations representing 48 patients).

1 INTRODUCTION

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) has received a literature-based NDA (203629) for neostigmine injection, a currently marketed unapproved drug product. The sponsor's (APP Pharm) proposed indication is for reversal of neuromuscular blockade. No new clinical safety or efficacy studies have been conducted for this application. Safety-related information from the sponsor's proposed label is in Appendix 8.1. DPV-2 has reviewed neostigmine adverse events (AEs) from AERS and the published literature in order to determine if there is any new safety information that should be incorporated into the sponsor's proposed neostigmine label.

2 METHODS

2.1 AERS SEARCH STRATEGY

The Adverse Event Reporting System (AERS) was searched as shown in Table 2.1

Table 2.1 AERS Search Strategy*	
Date of search	1/25/12
Time period	1/1/69 to 1/25/12
Product Term	Neostigmine (active ingredient search)
MedDRA Search Terms	None; all events were retrieved

*See Appendix 8.5 for the description of the AERS database.

2.2 LITERATURE SEARCH

The literature search was conducted as shown in Table 2.2

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

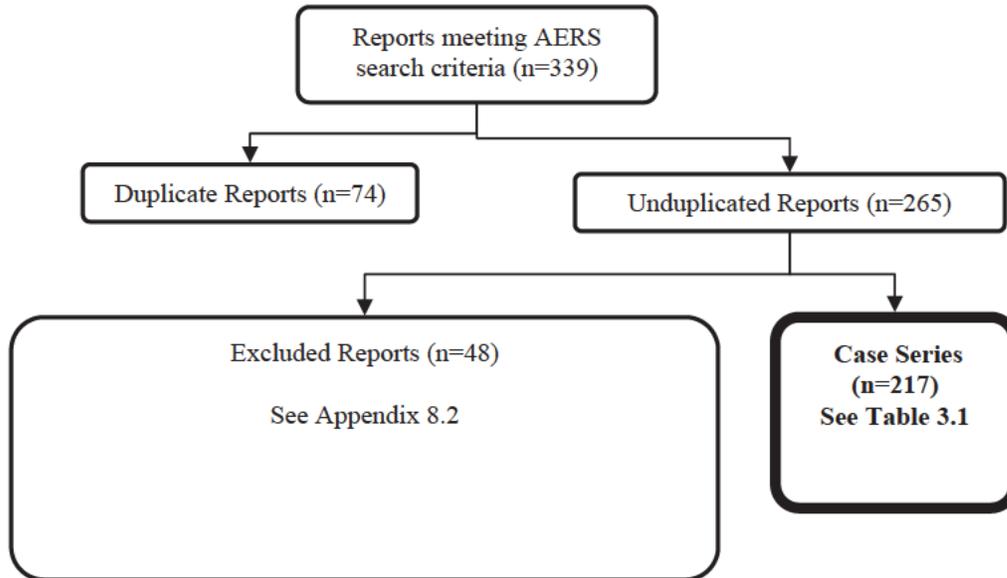
We retained for further review literature case reports and reports of deaths in clinical studies that had not been submitted to the NDA or to the postmarketing adverse event reporting system (AERS).

3 RESULTS

3.1 AERS CASES

3.1.1 AERS CASE SELECTION

Figure 3.1.1 AERS CASE SELECTION



The analysis of all events reported in this case series did not find any new safety issue for which the proposed label can be strengthened or new events could be added. Confounding factors in AERS cases include concomitant medications, medical history (surgical or procedural complications occurring before neostigmine administration), and/or the lack of sufficient clinical information.

3.1.2 LABELED EVENTS FROM AERS FOR ALL INDICATIONS

The most commonly reported indication in our neostigmine AERS case series (n=217) was neuromuscular blocker (NMB) reversal (n=150; 69%). The remaining cases reported other (n=47; 22%) or unknown indications (n=20; n=9%). Almost one-half (21/47; 45%) of the 'other' indications were for GI tract stimulation; the remaining were amenorrhea (12), myasthenia gravis (9), spinal anesthesia (3), and urinary retention (1).³

There were 726 reported events for all indications, approximately half of which are labeled. (Table 3.1.2.1)

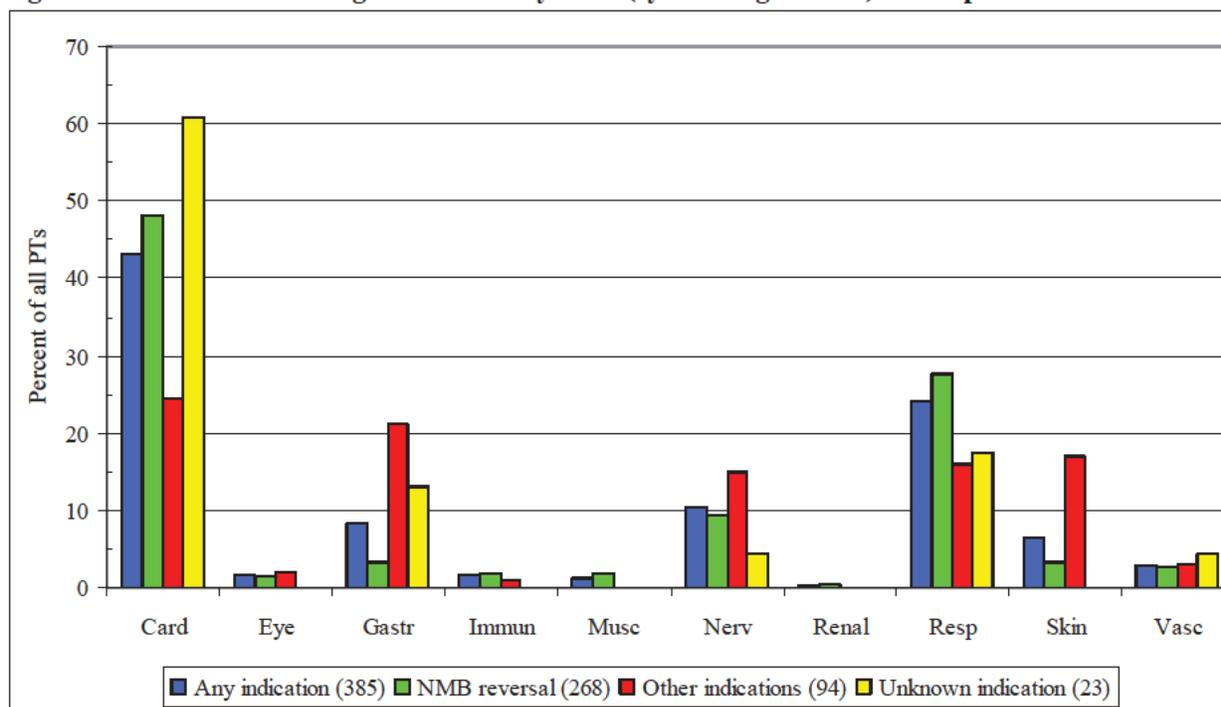
³One of the 47 'other' indications was inadvertent neostigmine administration (medication error).

Table 3.1.2.1 All events by reported indication and label status

Indication	Events	Labeled	Unlabeled
NM reversal	512	268	244
Other	174	94	80
Unknown	40	23	17
Total	726	385	341

The *labeled* events (n=385), by reported indication, are shown in Figure 3.1.2.

Figure 3.1.2. Labeled neostigmine events by SOC (system organ class) and reported indication



Across all indications, the three most common groups of events (in descending order) were cardiac, respiratory and nervous. There was a disproportionate number of reported events for “*other indications*” under gastrointestinal, nervous and skin SOC. This is due to a cluster of 10 cases where neostigmine was used for amenorrhea in patients who experienced (and recovered from) ‘dysphagia, nausea, cold sweat and asthenia’ after the administration of the drug.

The labeled events as PTs (preferred terms) are listed in Table 3.1.2.2.

TABLE 3.1.2.2 LABELED EVENTS AS PTS⁴ BY INDICATION⁵

	Reported indication		
	NMB Reversal	Other	Unknown
SOC (All)	268	94	23
Cardiac SOC (All)	129	23	14
Cardio and/or respiratory arrest	27	4	9
Bradycardia or decreased heart rate	23	8	
Tachycardia or heart rate increased	19	2	
Arrhythmias (ventricular, atrial, NOS)	18	2	2
Hypotension or blood pressure decreased	14	4	1
Atrioventricular block	13		1
EKG abnormal	10		
Myocardial infarction	2		
Resp SOC (All)	74	15	4
Oxygen saturation decreased/hypoxia	15		
Respiratory arrest, depression, distress or failure	13	3	2
Dyspnoea or apnoea	12	3	1
Bronchospasm or laryngospasm	7	4	1
Respiratory acidosis	4		
Cyanosis	3	2	
Hypercapnia	3		
Increased bronchial secretion/laryngoedema	3		
Stridor or wheezing	3		
Cough	2		
Hypoventilation	2		
Respiration abnormal	2	1	
Nervous SOC All	25	14	1
Sedation, somnolence or asthenia	10	11	1
Coma or LOC	7	1	
Convulsion	3		
GI SOC (All)	9	20	3
Nausea or vomiting	4	11	2
Abdominal pain/pain	2	2	
Diarrhoea	2	3	
Skin SOC (All)	9	16	
Rash/erythema/urticaria	7	3	
Vascular SOC (All)	7	3	1
Shock/circulatory collapse	5		1
Flushing	2		
Immune SOC (All)	5	1	
Anaphylaxis/hypersensitivity	5		
Musc SOC (All)	5		
Muscle spasms/twitching	4		

⁴Blank cells mean zero reports.

⁵Within any particular SOC, related-PTs were grouped together. For NMB reversal, PTs with a single report are not listed.

	Reported indication		
	NMB Reversal	Other	Unknown
Eye SOC (All)	4	2	
Miosis/visual changes	4	2	

3.1.3 NMB REVERSAL (n=150)

Demographic and other information from the cases reporting neostigmine use for NMB reversal are in Table 3.1.2.3

Table 3.1.2.3 Descriptive characteristics of AERS neostigmine cases for NMB reversal (n=150)	
Age (132)	Mean (46.6); median(49.5); range (2 months to 87 years); pediatric (15)
Sex (135)	Female (69); male (66)
Received year (150)	1970's (4); 1980's (5); 1990's (34); 2000's (80); 2010-11 (27)
Country (150)	U.S. (89); foreign (61)
Report type (150)	Direct (51); periodic (8); expedited (91; literature [39])
Serious Outcomes (126) ⁶	Death (18); hospitalization (46); life-threatening (29); disability (5); Other (63)
Recovery [for non-fatal, (132)]	Yes (104); no (1); unknown (27)
Time to event onset [excluding drug ineffective, (95)]	<60 minutes : <60 (n=53; range 1 to 45 min) ≥1 and <24 hours : (n=30; 1 to 20 hours) ≥1 day : (n=12; 1 to 7 days)
Dose (57)	Within recommended: yes (51); no (6; [low 4], high [2])
Procedure (101)	Top 3: GI/abdominal (43); ENT (15); reproductive (12); complete list of procedures is in Appendix 8.4
Anticholinergic co-administration (100)	Glycopyrrolate (64); atropine (36)
NMB that neostigmine reversed (132) ⁷	Vecuronium (39); rocuronium (34); succinylcholine (20); atracurium (19); pancuronium (7); cisatracurium (5) curare-related (4), ⁸ mivacurium (3); doxacurium (1); alcuronium (1)

the 18 fatalities (adult, n=17; unknown age, n=1). Most of the fatalities (13/18; 72%) were caused by cardio and/or respiratory arrest (labeled); three other cases were due to agranulocytosis,⁹ anaphylaxis, and multi-organ failure (MOF), respectively. The MOF case (54-year-old female) was confounded by ~25% of her body being burned in a house fire and having received 27 other drugs besides neostigmine.¹⁰ In the

⁶Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events; *Cases are not mutually exclusive.*

⁷Not mutually exclusive.

⁸d-tubocurarine (3); curare (1).

⁹Although the role of neostigmine cannot be excluded, this 68 year-old female underwent mastectomy and contributing factors could have been any prior breast cancer treatment (e.g. chemotherapy, radiation). Agranulocytosis onset was on Day 8. (neostigmine given on Day 1) and death was on (b) (6) during which time other unknown factors could have contributed.

¹⁰Literature report: Kitamura R, Takeda A, Uchinum E. A case of burn with toxic epidermolysis. *Jap. J. Burn Injuries* 2008;34:89-85.

remaining 2 cases, where the cause of death was not reported, contributing factors were age (75, 87 years), cardiovascular disease (both) and cancer (lung and lymphoma, respectively).

Where known (n=12), 9 patients died within a few days (2-5 days; n=4)¹¹ to weeks (2-6 weeks; n=5) after neostigmine administration. It is unlikely that a short acting drug like neostigmine could have contributed significantly to the deaths in many of these cases. One of the 9 patients was an 84 year-old female who underwent an unknown procedure, and it was uncertain if she received glycopyrrolate, which was ordered by her physician to counter neostigmine-induced bradycardia. Not receiving this drug could have contributed to the patient's cardiac arrest.

Although, in the remaining 3 of 12 cases, fatal cardio-respiratory arrests¹² occurred on the same day as neostigmine administration, they were all confounded. Two had cardiovascular disease; in the third case, the contributory role of neostigmine could not be discerned from the other concomitant anesthetics administered. Where known (n=4), most (n=3) of the neostigmine dosing was according to the label.¹³

There were 15 pediatric cases. Two-thirds of the patients (n=10) experienced cardiac and/or respiratory events (n=7) or hypersensitivity reactions (n=3) which are labeled¹⁴. In 2 of the cases with cardiac and/or respiratory events (involving 3 and 16 year-olds), their underlying conditions (AV conduction abnormality¹⁵ and Brugada syndrome¹⁶ respectively) were contributory factors. Four other patients experienced somnolence (1), amnesia/visual acuity reduced (1), aggression/sleep disorder (1), and proteinuria/hematuria (1) respectively; in all cases, there were other drugs and/or an underlying medical condition that could have contributed. The last case involved a 13-month old female, who received a slightly higher (1.14 times) than the recommended dose, and recovered from her extended period (3.5 hrs) of post surgical paralysis (lack of effect). Where known (n=13), all but one¹⁷ recovered from the reported events. Patients' age ranged from 2 months to 16 years; median was 6 years. The most common procedures (n=9) were ENT (n=4) and GI/abdominal (n=3). Neostigmine dosage (n=7), was mostly (n=6) according to the label.

Sixty-nine percent (103/150) of the cases reported unlabeled events. Table 3.1.2.4 lists the unlabeled events *that have a count of 2 or more cases*.

Table 3.1.2.4 Unlabeled events (n≥2) reported with neostigmine use for NMB reversal

SOC	Events
Blood (12)	Lymphocyte abnormalities (2); hemoglobin changes (2); decreased protein parameters (2); coagulation abnormalities (2)

¹¹In one, a medication error was suspected as glycopyrrolate was intended to be given, but may not have been administered.

¹²Autopsy for one said cause of death was myocardial infarction.

¹³A 47-year-old 48 kg male (experienced cardio-respiratory arrest; history of hypertension and asthma) received 1.26 times the maximal 40 mcg/kg labeled neostigmine dose after having plastic surgery. This patient was given *three* NMB's (succinylcholine, mivacurium and doxacurium) which may explain the excessive neostigmine dose.

¹⁴Or can be a consequence of a labeled event.

¹⁵Heard CMB; perioperative considerations in a newly described subtype of congenital long QT syndrome; *Paed. Anaesthes.* 1998;8:93:96.

¹⁶Kloesel B, Ackerman J, Sprung J, Marr, BJ, Weingarten TN. Anesthetic management of patients with Brugada syndrome: a case series and literature review. *Can. J Anesthes* 2011;58:824-836. From Kloesel 2011: Brugada syndrome manifests as ECG changes (e.g. ST elevation and incomplete bundle branch block). Brugada syndrome is often associated with syncope and sudden death.

¹⁷A 6-year-old (with a history of flu, fever and cough 2 weeks prior) became comatose after an appendectomy; limited information prevents any further assessment.

Cardiac (15)	Blood pressure increased (11)
Gastrointestinal (7)	GI hemorrhage (2)
General (61)	Drug ineffective (36) ¹⁸ ; 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 ¹⁹ (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)

Adverse events from the General SOC (62 PTs; n=50²⁰) and Injury and poisoning SOC (35 PTs; n=29) were the most commonly reported.

For the General SOC, Drug ineffective (n=36 PTs; n=31) was the most reported event²¹ which occurred throughout the past 22 years (1990-1999, n=13; 2000-2012, n=18). There was no mention of any pharmaceutical testing data for any of the 31 drug ineffective cases. In most (6/7) of the drug interactions, there were multiple medications administered and there was no pharmacological basis for neostigmine's involvement in the case (e.g., in one case,²² paroxetine and fentanyl were most likely responsible [for the serotonin syndrome]). The last drug interaction case (prolonged neuromuscular block) reported the use of neostigmine and donepezil (also an anticholinesterase). The patient received succinylcholine (followed by pancuronium); however, the patient's low pseudocholinesterase level was a confounder.

For the Injury and Poisoning SOC the following PTs were most commonly reported: *post procedural complication, delayed recovery from anesthesia and/or prolonged NM block or anesthetic complication*. In most (n=18) cases, the reported PTs in this SOC did not add any clinical information to the other more specific PTs reported in the same case (e.g. in one case, the reported event 'cardiac arrest' was the *post procedural complication*). There were 6 cases where the Injury/Poisoning SOC terms (*delayed recovery from anesthesia and or prolonged NM block*) were the only terms describing the delayed response to NMB reversal.

¹⁸Includes the following PTS: drug effect decreased, drug effect delayed, drug ineffective, drug resistance, product quality resistance, therapeutic product ineffective, drug effect increased, and drug effect prolonged. The last two terms (n=2, n=1 respectively from 3 patients) referred to an excessive effect of the NMB. Neostigmine was also reported as a suspect drug, in addition to the NMBA decreased effect of neostigmine could not be excluded.

¹⁹Includes PTs: anxiety, irritability, listless, restlessness, stress

²⁰The second 'n' is the number of cases (patients).

²¹29 US and 2 foreign.

²²One was literature report: Gokcinar D, Karabeyoglu I, Ucar H, Gogus N; Postoperative nystagmus and anisocoria due to serotonin toxicity; *Acta Anaesthes. Scand.* 2006;53:694-695.

There were 4 cases that were coded as medication errors; one was fatal (mentioned above). Another case (dyspnea) claimed that the vial did not contain neostigmine, there was no testing done to confirm. The remaining 2 cases reported bradycardia and tachycardia, respectively; the first case reported neostigmine contamination of atropine (via use of the same needle during preparations) and the second case reported that neosynephrine was mistakenly given with neostigmine.²³

3.1.4 OTHER INDICATIONS (n=47)

Thirty-seven of 47 cases (78%) reported unlabeled events. Table 3.1.2.5 lists unlabeled events *that have a count of 2 or more cases*.

Table 3.1.2.5 Unlabeled events (n≥2) for other indications

SOC	Events
Cardiac (3)	Blood pressure increased (2)
Gastrointestinal (31)	Dysphagia (11); diverticular or intestinal perforation (4); abdominal infection (3); oral lesion (3)
General (8)	Drug interaction (2); multi-organ failure (2)
Injury and poisoning (11)	Medication error-related (4); anesthetic complication (3); procedural complication (2)
Renal (4)	Renal failure (3)
Respiratory (5)	Pneumonia (2)

Two SOCs, Gastrointestinal (31 PTs; n=19) and Injury and poisoning (11 PTs; n=9), contained the most unlabeled events. The most commonly reported event in Table 3.1.2.5 is *dysphagia*, which has been explained in Section 3.1.2. Two of the diverticular/intestinal perforations are discussed below (fatalities). The remaining two perforations were more likely due to other drugs (sodium polystyrene sulfonate/sorbitol and thiopental,²⁴ and prednisolone²⁵, respectively).

One of the 2 medication errors (4 PTs; n=2) is described below (fatality). The other case involved a 64-year-old female with ileus who received neostigmine 3 mg instead of 1 mg; she recovered from her bronchospasm.

There were seven fatalities, 6²⁶ involving medical use and 1 involving an inadvertent administration. The reported neostigmine indication (n=6) was GI tract stimulation (GTS, n=5) and myasthenia gravis (n=1). All had confounding medical history and/or concomitant medications as mentioned below:

More than half (n=4) were due to respiratory-related causes including pulmonary edema, bronchial pneumonia, pulmonary embolism (all unlabeled) and cardio-respiratory arrest (labeled). Each of these 4 cases had contributing medical history including cardiac failure, pulmonary embolism, emphysema, and/or pneumonia. Two patients died from multi-organ failure (MOF;

²³3 neostigmine ampules were intended to be used; 2 of the 3 vials erroneously ended being neostigmine.

²⁴Trottier V, Drolet S, Morcos MW. Ileocolic perforation secondary to sodium polystyrene sulfonate in sorbitol use. *Can. J. Gastroentero* 2009;10:689-690. This patient's refractory seizures were treated with a 2 day thiopental infusion. Ileus has been reported to occur after this barbiturate coma-treatment.

²⁵Mariasy R, Shapiro A, Mitchell T. Bowel perforation in a patient receiving prednisolone for myasthenia gravis. *Post Grad Med J.* 1989;65:428-429

²⁶All were adults; age known for 4: median 71 years; range 52 to 91 years.

n=2). In one MOF²⁷ (GTS, indication), contributing factors were suspected prior GI-tract stenosis and concomitant lactulose administration.²⁸ The other MOF involved a medication error and a 1-day old infant,²⁹ born with pulmonary stenosis. Neostigmine (Prostigmin) was given to the mother prior to birth instead of dinoprostone (Prostine). The last fatality (GTS, indication) was due to intestinal perforation for which the reporters stated was more likely due to prior radiation therapy and antineoplastic toxicity than neostigmine.³⁰

The time of neostigmine administration to death was reported in 5 of 7 cases as same day (n=3), 1 week (n=1) and 35 days (n=1). The case with the longest duration (35 days) involved a 61-year-old male who received neostigmine infusion for 10 days during which time he experienced cardiac and renal events; he died 25 days after the end of the infusion. The patient had contributing medical history that included colon cancer, cirrhosis, pancreatitis, and hypertension.

There were 3 pediatric cases (one fatal, mentioned above). The remaining 2 cases were confounded by contributing medical history (yes, n=1; unk, n=1) and other medications (n=2).

In the second case, a 3 month-old male (unknown medical history) received a 73 mcg/kg neostigmine dose s.c. to stimulate peristalsis and experienced bradycardia and cyanosis and recovered. Chloramphenicol eye drops, which could have contributed to the event, were also given.

In the 3rd case, an attorney reported that a pediatric patient (age unknown) has multiple malformations and chromosomal abnormalities including *Mobius syndrome* from *in-utero* exposure to neostigmine, medroxyprogesterone, and tetracycline, that were all taken within an 11 day period.³¹ The mother had a history of pelvic inflammatory disease and received neostigmine for ‘last menses’. This case was from 1986 and the ‘delayed menstruation’ was treated with neostigmine, due to the drug’s cholinergic effect on the uterine endometrium.³²

3.1.5 INDICATION UNKNOWN (N=20)

Ten of 20 cases (50%) reported unlabeled events.

Table 3.1.2.6 lists these unlabeled events *that have a count of 2 or more cases*.

²⁷Literature report: Mollema R, Spijkstra JJ, Polderman KH, Gelissen HP, Girbes AR. Perforation of the colon after administration of neostigmine. *Intensive Care Med.* 2004 Apr;30(4):730. Epub 2004 Feb 24.

²⁸Neostigmine is labeled as contraindicated in patients with... mechanical obstruction.... Lactulose can be associated with intestinal obstruction: van der Spoel JI, Oudemans-van Straaten HM, Kuiper MA, van Roon EN. Laxation of critically ill patients with lactulose or polyethylene glycol: a two center randomized, double-blind, placebo-controlled trial. *Crit. Care Med.* 2007;35:2726-2731.

²⁹All of the other fatalities were adults (age known for 4: median 71 years; range 52 to 91 years).

³⁰Literature report: Takashita atsushi, Akutagawa Kan, Noda Nachiro et al. an autopsy case of localized hepatic atrophy with veno-occlusive disease after radiation therapy. Western regional meeting of the Japan Society of Hepatology Dec 7-8, 2001; *Acta Hepatologica Japonica* 2002; 42 (S2) 583

³¹Drug(s) exposure was about 12 weeks after mother’s last menstrual period.

³²Soskin S, Wachten H, Hechter O. The treatment of delayed menstruation with prostigmine. *JAMA* 1940; 114:2090-2091.

Table 3.1.2.6 Unlabeled events (n≥2) for unknown indication

SOC	Events
Injury and poisoning (3)	Overdose (2) ³³
Psychiatric (4)	Completed suicide (3)
Renal (2)	Renal failure or tubular necrosis (2) ³⁴

Almost one-half (9/20) of the cases were fatal:

All 9 cases had one or more confounding factors of medical history (yes, n=3; unknown, n=6) and contributing other medications (yes, n=5; unknown=4). The time of neostigmine administration to death was reported as same day (n=2) and 14 days (n=1); this information was not provided in the remaining 6 cases.

Most (n=7) of the deaths were due to cardio and/or respiratory arrest (CRA). In 1 of 7 cases, a 41-year-old male committed *suicide* from an acute multi-drug exposure that included neostigmine.³⁵ The other drugs were mostly anesthesia-related.³⁶ Two of 7 were pediatric cases: A 5-month old (unknown sex and weight) who had a history of ‘not thriving’ and was alkalotic had an ‘upper GI series’; the patient received 0.15 mg neostigmine i.m.³⁷ The autopsy found the endotracheal tube in the esophagus. The second pediatric case involved a 16-year-old who committed *suicide* from multi-drug ingestion (including neostigmine [dose form and dosage unknown]³⁸).

Neostigmine appeared to be used ‘medically’ in 3 other CRA cases (GI-procedure, n=2³⁹). These cases were confounded by multiple concomitant medications, renal impairment (CrCl 25 mL/min), and unknown medical history. The last CRA lacked sufficient clinical information to determine whether neostigmine was used for medical or non-medical use, as well as if there were other confounding factors.

Two fatalities were not coded as due to cardio-respiratory arrest: A 45-year-old female committed suicide by overdose of neostigmine (dose form and dosage unknown) and methyldopa. A 25-year-old male had toxic epidermal necrolysis⁴⁰ after receiving neostigmine i.v. and 19 other drugs and subsequently died (unknown time and cause).

³³Single patient, fatal.

³⁴Single patient, non-fatal. The 64-year-old male experienced non-fatal renal failure and tubular necrosis 5 days after neostigmine administration, Unknown medical history, administration of other anesthesia and atracurium (for an unknown indication) over the 5 days were confounding factors.

³⁵Bronstein AC, Spyker DA, Cantilena LR, Green JL et al. 2007 Annual Report of the American Association of Poison Control Centers National Poisoning and Exposure Database (NSPDS) 25th Annual Report; Clin Toxicol 2008;46:927-1057.

³⁶Propofol, succinylcholine, cisatracurium, midazolam and venlafaxine.

³⁷Although it is possible that neostigmine was used to stimulate the gut for the GI procedure, there was a lack of any specific information regarding the indication.

³⁸Litovitz TL, Klein-Schwartz W, Rodgers GC, Cobaugh DJ et al. 2001 Annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System; Am. J. Emerg. Med. 2002;20:391-452.

³⁹It was not known if neostigmine was used as part of the anesthetic regimen or for another use (treating the GI-related condition (e.g. ileus).

⁴⁰Also coded as dermatitis exfoliative.

3.2 LITERATURE SEARCH

On March 28, 2012 we searched PubMed for English-language literature using “neostigmine” in the title and the word “adverse” as an unrestricted search term. We retained for further review case reports and reports of deaths in clinical studies that had not been submitted to the NDA or to the postmarketing adverse event reporting system (AERS). The search resulted in 52 reports of cases, ranging in publication date from 1948 through 2011, including 2 death cases found in references. The plurality of these (23) concerned patients who received the drug for the reversal of a nondepolarizing neuromuscular block after surgery. The most common nonindicated use was treatment of nonmechanical intestinal obstruction (15 reports); others included test dose after cardiac transplantation, reversal of depolarizing neuromuscular blockade, treatment of puffer fish poisoning; use in myasthenia gravis, overdose of neostigmine; in one case, the indication was unclear.

The adverse events reported in association with neostigmine, either the indicated use or various nonindicated uses, were labeled events or consistent with labeled events. These included asystole, bradycardia, atrioventricular block, hypotension, excess salivation, and nausea, abdominal pain, anaphylaxis, and bronchospasm. One of the cardiovascular reports was a fetus who experienced a drop in heart rate, with no other adverse event, after the mother was treated with neostigmine. In addition, cases were reported of increased or decreased pharmacological effects attributed to renal failure (5 patients), hypokalemia, 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.

The following are the deaths reported in the PubMed search. Two of the cases involved indicated use, one in a patient with a neuromuscular disease. Three were reported in patients receiving neostigmine for nonmechanical intestinal obstruction. In all of the fatalities, except the one preceded by bradycardia, the cause of death was not proximal to the administration of neostigmine.

- Buzello et al. (1982) report the death of a 57 year-old woman with dystrophia myotonica who died of bronchopneumonia, hypoxemia, hypercapnea, and recurrent bradyarrhythmia approximately 3 weeks after neostigmine had been given for a proposed indicated use, reversal of pancuronium neuromuscular blockade following a cholecystectomy. She had been extubated at 5 days following her procedure, then reintubated 12 hours later.

Comment: This death occurred in a patient with neuromuscular disease, and it occurred weeks after reintubation.

- Middleton (1957) report a death of a patient from shock 23 hours after reversal of apnea with neostigmine during surgery for a gunshot wound to the abdomen. The authors did not attribute the death to neostigmine, but concluded that neostigmine had reversed apnea that they attributed to neomycin.
- Van der Spoel et al (2001) reported the death of a patient with endocarditis and multiple organ failure treated in a clinical study with neostigmine (0.4-0.8 mg/hour for 24 hours) for colonic ileus who died with intestinal necrosis on day 7 after inclusion into the study. The authors state, “At this stage, no conclusions can be drawn regarding the risks and benefits of neostigmine on colon (micro-circulation)” and that “continuous infusion of 0.4-0.8 mg/h of the neostigmine promotes defecation in the critically ill, ventilated patients with an ileus of the colon, and is well-tolerated.”

An additional two deaths were reported in literature and referred to in the AERS case series. Both were in patients treated for nonindicated uses, and in both cases, the death followed a pharmacologically known effect of neostigmine.

- Briggs (1969) reported the death of a 9 year-old girl who had been treated with neostigmine, 15 mg daily for 2 years for megacolon, who became apneic and died. The author postulated that the underlying condition caused an accumulation of neostigmine and resulted in an overdose.
- Merrill (1948) reported the death of a patient with myasthenia gravis who died after a test dose of neostigmine. The death was preceded by bradycardia.

Reviewer's comment: The review of adverse events, including deaths, in our literature search did not uncover new safety concerns not addressed in the proposed label.

4 DISCUSSION

Our AERS review examined all neostigmine adverse events reported over the past 40 years in an effort to provide a comprehensive assessment of the spontaneous postmarketing safety data. We did not restrict our search for any particular type of 'indication'⁴¹ and our finding that most of the reported use was for NMB reversal makes our data more applicable for the sponsor's NDA application for the same indication. The larger proportions of *labeled* events in the cardiac, respiratory and nervous SOCs are compatible with the cholinergic activity of neostigmine. Our review of all unlabeled events did not find any that were compelling enough to be a new 'signal', requiring addition to the proposed neostigmine labeling.

The published literature search of adverse events reported in association with neostigmine, either for NMB reversal or various nonindicated uses, primarily retrieved labeled events and deaths due to various causes that appeared to be unrelated to neostigmine. The review of these adverse events, including deaths, did not reveal any new safety concerns not addressed in the proposed label.

5 CONCLUSIONS

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

6 RECOMMENDATIONS

DPV will continue routine monitoring of all adverse events reported in association with neostigmine.

⁴¹Neostigmine is currently an unapproved product.

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8 APPENDICES

8.1 NEOSTIGMINE LABELING (SAFETY RELATED INFORMATION)

SOC	Event
Card	atrioventricular block (as arrhythmia)
Card	bradycardia (as arrhythmia)
Card	cardiac arrest
Card	cardiac arrhythmias
Card	electrocardiogram changes (non specific)
Card	Hypotension
Card	nodal rhythm (as arrhythmia)
Card	tachycardia (as arrhythmia)
Eye	miosis
Eye	visual changes
Gastr	Emesis
Gastr	Flatulence
Gastr	Nausea
Gastr	oral secretion (as increased)
Gastr	peristalsis (as increased)
Genrl	death (overdose)
Genrl	drug interaction (certain aminoglycosides)
Genrl	Headache
Genrl	Weakness
Immun	allergic reaction
Immun	Anaphylaxis
Musc	Arthralgia
Musc	muscle cramp
Musc	muscle spasm
Musc	muscle weakness (overdose)
Nerv	cholinergic crisis (overdose)
Nerv	Convulsions
Nerv	Dizziness
Nerv	Drowsiness
Nerv	Dysarthria
Nerv	loss of consciousness
Renal	urinary frequency
Resp	bronchial secretions (as increased)
Resp	Bronchospasm
Resp	Dyspnea
Resp	pharyngeal secretion (as increased)
Resp	respiratory arrest
Resp	respiratory depression

SOC	Event
Resp	respiratory impairment (via muscles, overdose)
Skin	Diaphoresis
Skin	Rash
Skin	Urticaria
Vasc	Flushing
Vasc	Syncope

8.2 EXCLUDED AERS CASES (N=48)

Reason for Exclusion	N
Neostigmine not administered	18
Event occurred before neostigmine administration	7
Not enough info to determine nature of event	5
Cannot determine relationship of neostigmine and event	5
Image illegible or not available in AERS	4
Not likely due to neostigmine because of long time to onset	3
Event most likely related to another drug	3
Ophthalmic neostigmine not likely cause of systemic or generalized event	2
Fictitious patient	1

8.3 PROCEDURES FOR NMB REVERSAL (N=101)

Procedure	N
GI/abdominal	43
ENT	15
Reproductive	12
Musculoskeletal	9
Urogenital	8
Cardiovascular	6
Respiratory	4
Skin	3
Normal volunteer	1

8.4 ADVERSE EVENT REPORTING SYSTEM (AERS)

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance (ICH E2B) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

8.5 AERS CASE, ISR AND MANUFACTURER CONTROL NUMBERS

CASE	ISR	MFRCTRL
3005963	3014720	PROST.TAB.-FRAN-121997-0001 ⁴²
3018904	3180797	8-98030-007L
3022400	3070795	A001-002-001828
3025606	3006429	
3029166	3021881	
3073248	1999924	897205001J
3115839	3021883	
3115840	3021880	
3115847	3021877	
3326614	3326390	
3347545	3514523	104776
3410547	3436635	PRIUSA1999009423
3420719	3443508	217473
3437286	3461311	
3457136	3488859	A010568
3468195	3496208	
3526803	3566948	JP NSI 0807000001
3546840	3584906	
3551295	3592035	2000-09-1530
3551482	3587534	
3635213	3694420	
3652941	3720912	
3704763	3786619	01H-163-0110095-00
3720997	3823415	PHHO2001AU07677
3744315	3843958	01-0096
3745837	3871448	200120807JP
3767938	3875299	1553-012-1
3768211	3875297	1553-012-2
3773838	3883747	02-004
3816275	3947191	CTU 172154 Dir
3824311	3953254	M0638-2002
3895983	4048086	03H-008-0208314-00
3905328	4055898	2003002648
3953254	4119167	CTU 193944 Dir

⁴²For direct reports, mfr control number is blank or ends in 'Dir'. NA (not available) are periodic reports (received 1969-1973) for which the sponsor did not assign a mfr control number.

CASE	ISR	MFRCTRL
3959530	4135110	200311645EU
3970885	4146475	CTU 197863 Dir
4000611	4201609	200308764
4008941	4192818	M0943-2003
4032600	4230365	03H-163-0238550-00
4054864	4258936	03H-161-0244806-00
4054874	4258937	03H-161-0244804-00
4054883	4258938	03H-161-0244805-00
4093296	4302321	WAES 0402DEU00054
4111729	4319374	CTU 214651 Dir
4148288	4365346	04H-163-0260166-00
4182545	4410582	CTU 223765 Dir
4226128	535	NA
4226129	536	NA
4227283	1690	NA
4227284	1691	NA
4227285	1692	NA
4227291	1698	NA
4227292	1699	NA
4230692	5099	
4234624	9031	NA
4234625	9032	NA
4234627	9034	NA
4234628	9035	NA
4235554	9961	
4243486	17893	
4270457	45203	NA
4280280	55036	NA
4281282	56038	NA
4282013	56769	
4290893	65918	NA
4296598	72139	74137
4408409	190519	MS84415
4413146	304225	112
4454580	359169	
4546119	463997	670925 Dir
4604910	531331	111511839
4634763	565129	189004391
4652753	586050	E8907
4670276	605590	13718766
4684357	621571	1115890006P

CASE	ISR	MFRCTRL
4704801	645270	106890003P
4705419	645888	90071B
4706161	646848	90071A
4725250	668175	08338B Dir
4726209	669284	08338A Dir
4791105	742180	U010963 Dir
4809800	763236	910269001
4814785	768854	
4849589	807070	D107646 Dir
4861556	820675	
4882631	844640	6.203E+11
4973743	946330	ASHPCP Dir
5116237	1454654	
5118959	1457571	
5120250	1458948	
5120505	1459218	USA9400818PAM
5144726	1485241	MIVACRON489
5149979	1490927	9.40201E+11
5150995	1492000	9.40201E+11
5152064	1493123	894227003W
5180432	1523146	
5244393	1590200	
5254061	1600442	
5345927	1695412	
5346590	1696090	
5366637	1716609	
5375077	1725269	895335001N
5385159	1735664	896095005S
5424468	1776149	B0039903
5445400	1797828	
5451303	1803866	
5539359	1894619	
5672835	4530040	JP-BRISTOL-MYERS SQUIBB COMPANY-12763678
5778182	4633399	A500121004/LB-04-004
5820218	3286115	111815
5844742	671278	9.004E+11
5859786	4690009	2004-122342-NL
5859790	4690008	2004-122319-NL
5880110	4766852	LNL-100121-NL
5880113	4766854	LNL-100125-

CASE	ISR	MFRCNTRL
		NL
5941676	4850753	CTU 264656 Dir
5999525	5024732	805#1#2006- 00007
6008958	4940947	06H-066- 0305906-00
6031602	4975007	CTU 274327 Dir
6034521	5032697	2006AP01934
6034604	4975044	CTU 274310 Dir
6035235	4981830	CTU 274694 Dir
6036014	4980314	CTU 274797 Dir
6036018	4980315	CTU 274796 Dir
6058992	5025969	2006AP02484
6065172	5120300	JP-ABBOTT- 06P-087- 0335514-00
6073482	5026066	CTU 278697 Dir
6108948	5075754	ENT 2006-0104
6141359	3626963	FR NSI 111000 0003
6144072	5141479	2006AP04615
6152362	5130607	CTU 287356 Dir
6158455	3707417	256483
6158466	3614171	
6179374	5158150	CTU 289752 Dir
6201687	5190719	GB-PURDUE- GBR 2006 000 2705
6312207	5430328	PHBS2007JP08 026
6329232	5381771	JP-BRISTOL- MYERS SQUIBB COMPANY- 13805882
6337712	5357197	CTU 305441 Dir
6392467	5427513	SE-JNJFOC- 20070804000
6458578	4595046	2005VX000153
6458778	4635403	2005VX000275
6458780	4928963	FR- GLAXOSMITH KLINE- B0408169A
6458783	5480634	US-BAXTER- 2007BH008049
6458786	4738070	CTU 255563 Dir

CASE	ISR	MFRCNTRL
6458788	5482448	CA-MERCK- 0710USA01020
6458886	4595081	2005VX000154
6458887	4811538	2005VX000564
6458888	4891031	2006AP00336
6459892	5501424	CTU 316412 Dir
6517505	5573348	CTU 320779 Dir
6532356	5593372	2006VX001793
6535234	5614016	GB-ROCHE- 542689
6545667	5606116	2007VX003025
6591764	5668901	CTU 328444 Dir
6605646	5693995	US-BAXTER- 2008BH002822
6612074	5690341	CTU 330354 Dir
6614924	5689918	CTU 330627 Dir
6673205	5779819	GB- RANBAXY- 2008RR-15916
6680021	5772146	CTU 339684 Dir
6684397	5772007	CTU 339723 Dir
6684440	5772012	CTU 339721 Dir
6688137	5777948	CTU 340456 Dir
6707146	5809693	CTU 343071 Dir
6709330	5851983	JP-PFIZER INC- 2008060498
6722529	5828292	CTU 345065 Dir
6722573	5828293	CTU 345066 Dir
6722607	5828295	CTU 345064
6743891	5941970	JP-MERCK- 0808USA04635
6831566	6448876	2008BH003873
6869001	6013053	20080187 /
6872783	6027267	US- ASTRAZENECA- 2009AC00007
6882827	6036494	2008VX002621
6992551	6181074	CTU 375756 Dir
7047316	6264469	GB- ASTRAZENECA- 2009SE03816
7048465	6255556	20090221
7084490	6313368	"US-ROXANE

CASE	ISR	MFRCNTRL
		LABORATORI ES, INC.-2009- RO-00827RO"
7090882	6304933	20090326 /
7100156	6326338	20090364
7110158	6342207	CTU 390911 Dir
7110902	6348761	FR- ASTRAZENECA- 2009SE11653
7135682	6383243	"JP-ROXANE LABORATORI ES, INC.-2009- RO-00982RO"
7162929	6417721	CTU 396326 Dir
7218040	6470896	20090499
7276433	6578562	"CA-ROXANE LABORATORI ES, INC.-2010- RO-00143RO"
7325111	6614445	CTU 410145 Dir
7333529	6653902	"US-ROXANE LABORATORI ES, INC.-2010- RO-00319RO"
7337288	6623922	10TR001267
7356201	6683280	"NZ-ROXANE LABORATORI ES, INC.-2010- RO-00406RO"
7382047	6678855	2009BH005305
7382049	6678857	2009BH005307
7401992	6744745	AU-ABBOTT- 10P-008- 0646349-00
7410175	6756783	US-JNJFOC- 20100510839
7424796	6773656	CTU 421325 Dir
7426651	6781974	B0661328A
7441625	6801927	FR-BAXTER- 2010BH016560
7501506	6836768	20100280
7527581	6885301	CTU 425342 Dir
7545626	6955903	DE-WATSON- 2010-11101
7613979	7007572	2010SP046811
7766708	7208954	2010SP063814
7772670	7177109	CTU 438594 Dir
7915105	7437815	US-BAXTER- 2011BH011620
7920823	7795096	FK201100536
7921061	7795118	FK201100537
7931531	7439438	CTU 451416 Dir

CASE	ISR	MFRCTRL
8012317	7655513	2011SP025786
8012831	7577760	FR-VALEANT-2011VX000050
8031715	7604661	JP-MYLANLABS-2011S1013834
8062419	7641085	CTU 460306 Dir
8087186	7688808	CN-ASTRAZENECA-2011SE46231
8111108	7715804	US-FDA-7715804 Dir
8133153	7746391	US-FDA-7746391 Dir
8203454	7905231	GR-BAXTER-2011BH033458
8203455	7921524	GR-BAXTER-2011BH033459
8238316	7938423	US-WATSON-2011-18645
8238425	7934529	2011SP050712
8319331	8008736	2011MA017540

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Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date	May 25, 2012
Reviewer	Denise V. Baugh, PharmD, BCPS Division of Medication Error Prevention and Analysis
Team Leader	Lubna Merchant, PharmD, M.S. Division of Medication Error Prevention and Analysis
Associate Director	Scott Dallas, R.Ph Division of Medication Error Prevention and Analysis
Division Director	Carol Holquist, R.Ph. Division of Medication Error Prevention and Analysis
Drug Name(s) and Strength(s)	Neostigmine Methylsulfate Injection, USP 0.5 mg/mL and 1 mg/mL
Application Type/Number	NDA 203629
Applicant	APP Pharmaceuticals, Inc.
OSE RCM	2012-239

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1 INTRODUCTION

This review evaluates the proposed container label, carton and insert labeling for Neostigmine Methylsulfate Injection, USP for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND

Neostigmine Methylsulfate Injection, 10 mL vials are unapproved products available in concentrations of 0.5 mg/mL and 1 mg/mL and marketed under the names, “Neostigmine” and “Prostigmin”.

1.2 PRODUCT INFORMATION

The following product information is provided in the December 28, 2011 submission.

- Active Ingredient: Neostigmine Methylsulfate Injection, USP
- Indication of Use: reversal of nondepolarizing neuromuscular blocking agents (b) (4)
- Route of Administration: intravenous
- Dosage Form: Injection Solution
- Strengths: 0.5 mg/mL and 1 mg/mL
- Dose and Frequency: recommended doses range from (b) (4) to (b) (4) and should be given with appropriate doses of an anti-cholinergic agent (atropine or glycopyrrolate)
- How Supplied: 10 mL multiple dose vials
- Storage: 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature]
- Container and Closure System: The vials are closed with formulation (b) (4) gray (b) (4) rubber, serum stoppers provided by (b) (4) and capped with aluminum crimped flip cap sealed provided by either (b) (4) or (b) (4). The filled, stoppered, capped and (b) (4) labeled vials are then placed into (b) (4) uncovered trays.

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (AERS) database for Neostigmine medication error reports. We also reviewed the Neostigmine labels and package insert labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (AERS) using the strategy listed in Table 1.

Table 1: AERS Search Strategy	
Date	April 18, 2012 (with no time limitations)
Drug Names	active ingredient: Neostigmine verbatim term: Neostig% verbatim term: Prostig%
MedDRA Search Strategy	Medication Errors (HLGT) Product Quality Issue (HLGT)

The AERS database search identified 37 reports. Each report was reviewed for relevancy and duplication. After individual review, eighteen (n = 18) reports were not included in the final analysis for the following reasons:

- adverse event not related to a medication error;
- intentional overdose;
- product quality issues;
- medication error where neostigmine was not the source of the error; and
- duplicates

2.2 LITERATURE SEARCH

We searched the ISMP publications on April 18, 2012 for additional cases and actions concerning Neostigmine. There were no additional cases identified.

2.3 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted December 28, 2011 (Appendix B)
- Tray Labeling submitted December 28, 2011 (Appendix C)
- Insert Labeling submitted December 28, 2011 (no image)

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

2.4 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously completed an internal signal analysis involving label confusion (OSE 2008-22 dated January 15, 2008) between Neostigmine and Etomidate labels (manufacturers American Regent and Ben Venue Laboratories, respectively). We did not find similarity among the labels and there was no further assessment. Additionally, the signal case (ISR# 5545433-5) was found to be a duplicate of ISR# 6784647. ISR# 6784647 was included in the AERS cases evaluated for this review.

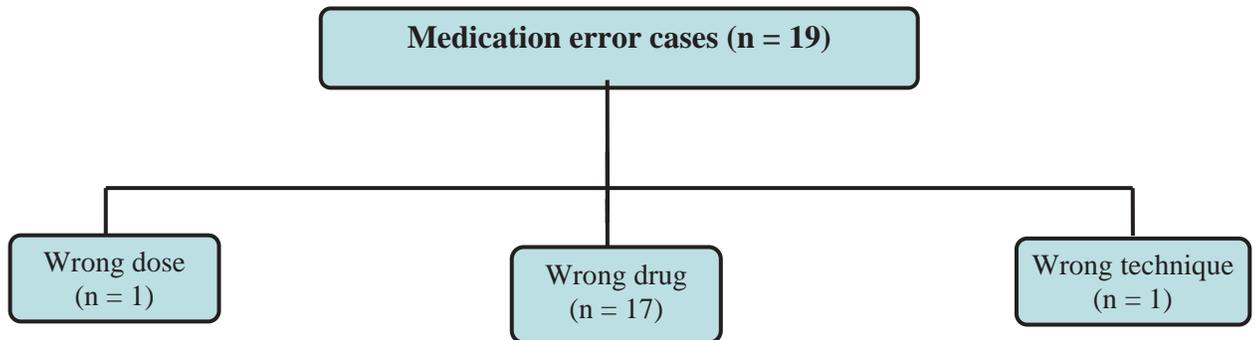
3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our AERS search and the risk assessment of the Neostigmine product design as well as the associated label and labeling.

3.1 MEDICATION ERROR CASES

Following exclusions as described in section 2.1, nineteen Neostigmine medication error cases remained for our detailed analysis. Duplicates were merged into a single case. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter². Figure 1 provides a stratification of the number of cases included in the review by type of error. Appendix D contains the ISR numbers and a detailed listing of the cases.

Figure 1: Neostigmine medication errors (N = 19) categorized by type of error



² The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>. Accessed June 1, 2011.

3.1.1 Wrong Drug Medication Error (N = 17)

We identified a total of seventeen (n = 17) wrong drug type cases. Of the seventeen cases, there were 8 complaints of similar looking vials causing confusion, and nine cases were actual errors (three of the errors were caught prior to administration to the patient). As stated, none of the seventeen cases identified APP pharmaceuticals as the manufacturer and no cases of wrong drug errors were retrieved from AERS beyond 2010.

Of the 9 errors, there was one isolated case where Pancuronium was given instead of Neostigmine (ISR# 4061834) and one report where Neostigmine was administered instead of Etomidate to two different patients (ISR# 3912492). Neostigmine and Etomidate were a source of confusion for another reporter on two separate occasions, but the difference was noticed prior to withdrawing the product from the bottle. Additionally, there were two foreign cases involving confusion between Neosynephrine and Prostigmin (ISR# 4923406 and 5545433) resulting in patient harm. In the remaining two (of the 9) cases, the intended medication was not stated (ISR# 5594017) or was unclear (ISR# 4005969), but these errors were caught prior to administration to the patient. Outcomes included increased monitoring (n = 2), ventilation (n = 1), blood pressure changes requiring intervention (n = 2) and unknown (n = 1). All reporters attributed their errors to similar looking vials and one reporter specifically cited the similar size (10 mL), lettering and color scheme as the cause for confusion.

Eight of the 17 cases were complaints of look-alike labeling/packaging. Six were single reports of confusion between Neostigmine and Leucovorin Calcium (ISR# 731017), Atropine (ISR# 3874961), Chromium Chloride (ISR# 4111786), Sterile Water for Injection (ISR# 4367881), Etomidate (ISR# 3972399), and Tensilon (ISR# 5212793). One case described a group of anesthesiologists who reported label confusion among three different products (Pancuronium, Glycopyrrolate, Aminophylline) and Neostigmine (ISR# 4169467). The remaining case cited label confusion between the two strengths of Neostigmine (ISR# 4811538).

Look-alike features of the products were stated to be vial size, similar color scheme, cap color, font size and type, and similar location of name. As stated above, none of these cases identified APP pharmaceuticals as the manufacturer.

3.1.2 Wrong Dose Medication Error (N = 1)

We retrieved one case (ISR# 7177109) where a patient received 3 mg of Neostigmine instead of the prescribed 1 mg for the patient. The patient developed shortness of breath, bronchospasm, and copious secretions which resolved with the administration of atropine. No contributing factors were cited in this case and the manufacturer of the Neostigmine was not identified.

3.1.3 Wrong Technique Medication Error (N = 1)

We retrieved one report where a caregiver administered a patient's Neostigmine with an insulin syringe. There was no patient harm and the cause of this wrong technique error was not stated.

4 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

In our evaluation of 17 cases of wrong drug cases and complaints of look-alike labels, the majority of reports involved actual or potential errors between Neostigmine and Etomidate and none of the reports involved APP Pharmaceuticals where the manufacturer was identified.

We compared the currently marketed labels for Etomidate by Bedford (ANDA 074593) and the proposed Neostigmine labels to assess their look-alike similarity and the potential for confusion since both products are available in the same practice setting (e.g., anesthesia department) and the majority of actual and potential errors have involved these two drug products. The labels are not similar and our concerns are minimized regarding confusion between these two labels. However, we note that the proposed neostigmine labels can be modified to improve the readability of important information and to bring the presentation of this information up to current standards.

5 CONCLUSIONS

DMEPA concludes that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of this drug product. See Section 6 below.

6 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. Container Label (10 mL vial, 0.5 mg/mL and 1 mg/mL)

1. Delete the  (b) (4)
2. Revise “I.V” to “Intravenous” to emphasize the proper route of administration of this drug product and to avoid dangerous abbreviations. This abbreviation may be misinterpreted as “I.U.” (for international units) and is therefore error-prone.
3. Revise the font size of the total drug content relative to the concentration in accordance with USP General Chapter <1> requirements. The total drug content should be more prominent. Additionally, include the total drug content and the concentration within the same color block. For example,

Neostigmine Methylsulfate Injection, USP

10 mg/10mL
(1 mg/mL)

4. Relocate the “Rx only” statement to the bottom right side of the principal display panel.
 5. Delete the extraneous numbers (e.g., “38210” and “38310”) located to the right of the NDC number at the top of the principal display panel to avoid confusion.
 6. Present each word in the statement “10 mL Multiple Dose Vial” in similar sized font.
- B. Tray Labeling (Ten 10 mL vials, 0.5 mg/mL and 1 mg/mL)
1. See A1 through A6.
 2. Combine the net quantity, vial size and packaging configuration into one statement. For example, “10 Multiple Dose Vials – Each vial contains 10 mL”. Use one font size for the entire statement.
- C. Insert Labeling
1. Revise the abbreviation “I.V” to read “Intravenous” throughout the labeling to reinforce the proper route of administration and minimize the risk of misinterpretation.
 2. Under the “Dosage Forms and Strengths” subheading (Section 3), revise the statement (b) (4) to read “0.5 mg/mL and 1 mg/mL” to accurately reflect the strengths.
 3. Under the “Dosage Forms and Strengths” subheading in the Highlights of Prescribing Information Section and in the “How Supplied” subheading 16.1) of the Full Prescribing Information section, delete (b) (4)

If you have further questions or need clarifications, please contact Danyal Chaudhry, OSE Project Manager, at 301-796-3813.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance ([ICH E2B](#)) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

2 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
immediately following this page.

Appendix D: ISR numbers of cases discussed in this review

ISR#, Date Reported, Age/Gender/Weight, Country	Type of Error	Cause	Outcome	Narrative
3912492, 06/10/02, Unknown/unknown/unknown, US 2 errors were cited in this case	Wrong drug	Look alike label	Monitoring	Neostigmine MS 1:100 10 mL vial (American Regent) was given to a patient instead of Etomidate 2 mg/mL, 10 mL vial (Bedford). Both vials are 10 mL and the lettering is gray and black with a white background. The vials look every much alike. The patient said “something is not right” and then he had to be closely monitored for several hours. This error occurred in 2 patients with 3 electroconvulsive procedures. After the error was discovered, pharmacy is now purchasing a different brand of neostigmine (with blue lettering).
4061834, 2/26/03, 51 years old, female, 140 lbs, US	Wrong drug	Look alike label	Ventilated in post op	At the end of an uneventful ureteroscopy the anesthesiologist mistakenly gave 5 mg Abbott Pancuronium instead of intended 2.5 mg Baxter Neostigmine. The look a-like vials contributed or caused the drug administration error. Patient was ventilated in post-op and later made a full recovery. Error was facilitated by the close resemblance of each vial. All paralyzing drugs should be packaged in distinctive vials with easily recognized colored labels.
5594017, 01/14/2008, Unknown, Unknown, Unknown, US	Wrong drug	Look alike label	Unknown	Pancuronium and Neostigmine were mixed up in an anesthesia procedure. The labeling is a different color but the vials are otherwise identical. The patient received the wrong medication.
4005969, 11/04/2002, Unknown/Unknown/Unknown (US)	Wrong drug	Look alike label	Error detected prior to administration	A pharmacist retrieved a box of neostigmine 1:1000 10-mL (Sicor generic) that was stored in the vicinity of, but not adjacent to, the TMP/SX stock. One vial of neostigmine was removed from the box and dispensed. The remainder of the neostigmine vials were placed in the TMP/SX fast-moving bin. The nurse who received the medication detected the error before it reached the patient because she noted that the TMP/SX vial was amber and neostigmine vials were clear. Although the two medications are packaged in differently colored vials, the boxes are nearly identical in appearance.

				This similarity seemed to confirm for the pharmacist that the right medication had been selected and the label was never read.
4923406, 02/22/2006, 28 years old/female/Unknown (FR)	Wrong drug	Look alike label	Patient entered a state of shock, manifesting a BP of 70/30mmHg and an HR of 120/min requiring intervention	Following a systematic analysis of the effects, a hypothesis involving the accidental injection of a vial of 1ml neosynephrine AP-HP (phenylephrine) at 5mg, has been accepted. Effectively, the space reserved for vials of prostigmine 1ml (0.5mg/ml) was contiguous with the space for neosynephrine 1ml (5mg/ml) in the anesthetic trolleys. A vial of neosynephrine was found among the vials of prostigmine, and they resemble one another both in form and labeling. At 12:30, as 2.5mg, that is, five vials worth, of prostigmine was being prepared, one of the vials used must have been neosynephrine. The direct intravenous injection of 5mg of neosynephrine can explain the observed clinical reaction in its totality
5545433, 12/06/2007, 23 years old/male/70 kg (FR)	Wrong drug	Look alike label	Blood pressure increase requiring intervention	French health authority reported several cases of drug administration error caused by confusion with Prostigmine 0.5mg/1ml solution for injection and Neosynephrine AP-HP 5mg/ml solution for injection ampoules. The administration drug error occurred because of confusion between both products. During drug preparation one or two ampoules of Neosynephrine were used and mixed with Prostigmine (confusion between the ampoules of Prostigmine). The patient presented with a brutal blood pressure increase, tachycardia and foaming expectoration. He received Lasix 40 mg, Risordan (isosorbide dinitrate) 0.9 mg/ml during 40minutes, glucose, KCl (potassium chloride) and Actrapid (insulin).
6784647, 06/22/2010, Unknown/Unknown/Unknown (US) 2 errors were cited in this case	Wrong drug	Look alike label	Error detected prior to administration	Near miss. I'm a CRNA. I wanted to draw up Neostigmine but accidentally put the needle in the Etomidate bottle. Didn't draw up the Etomidate but this is the second time I've almost made this error. The bottles look almost the same. Neostigmine is made by American Regent Inc (1:1000 concentration). The etomidate is made by Ben Venue labs, 20mg/ml. Both are 10 mL bottles with gray lids and similar labels.
731017, 03/14/1991, Unknown/Unknown/Unknown, (US)	Circumstances which have the capacity to cause error	Look alike label	None	Look alike packaging led to Neostigmine and Leucovorin Calcium found in same pharmacy stock bin. No doses given in error.

3874961, 02/25/02, 50 years old/female/Unknown (DE)	Circumstances which have the capacity to cause error	Look alike label	None	Anesthesiologist reported that the labeling for Atropine 1 mg/mL 1 mL vial (NDC 10019-251-12) and Neostigmine 1:2000 1 mL vial (NDC 10019-271-02), both of which are made by Baxter, have identical vial sizes and shape and white cap cover. Both have green bar labels and since both are part of the anesthesia cart, they can rest in holders and appear the same if the label is not carefully read. When looking on a side view from many angles, the vials are identical in appearance. We did not have an event occur, however, the nature of this look alike labeling can lead to a problem.
3972399, 09/06/2002, Unknown/Unknown/Unknown (US)	Circumstances which have the capacity to cause error	Look alike label	None	Bedford Lab's Etomidate 20 mg/10ml vial looks very similar to American Regent's Neostigmine 1:1000 10 ml vial. Both are stocked in Anesthesia carts. Both are white/gray labels with gray caps.
4111786, 05/12/2003, Unknown/Unknown/Unknown (US)	Circumstances which have the capacity to cause error	Look alike label	None	Potential look-alike error between Etomidate 20mg and Neostigmine methylsulfate 1mg/ml.
4169467, 08/15/2003, Unknown/Unknown/Unknown (US)	Circumstances which have the capacity to cause error	Look alike label	None	4 Vials reported by anesthesia staff to be "look alike" vials (Pancuronium 5 mL vial, Glycopyrrolate 0.2 mg/mL, 5 mL vial, Aminophylline 250 mg/10 mL, and Neostigmine 1:1000 1 mg/mL, 10 mL). Color coding pastel colors and not greatly different between drugs. Suggest Company use primary colors if going to color code vials.
4367881. 06/01/2004, Unknown/Unknown/Unknown (US)	Circumstances which have the capacity to cause error	Look alike label	None	Color band running down the middle of sterile water vial is pale green. Band color on Neostigmine is slightly darker green. A mix up between these two would likely be disastrous.
4811538, 10/25/2005, Unknown/Unknown/Unknown (US)	Circumstances which have the capacity to cause error	Look alike label	None	Confusion over look-alike similar packaging: Mfg: Baxter Neostigmine 1:2000 (0.5 mg/mL), 10mL MDV, NDC: 100019-271-37 (green label) vs. Neostigmine 1:1000 (1 mg/mL), 10mL MDV, NDC: 100019-270-39 (blue label)

5212793, 01/18/2007, Unknown/Unknown/Unknown (US)	Circumstances which have the capacity to cause error	Look alike label	None	The 10-mL vials of Prostigmin 1 mg/mL and Tensilon 10 mg/mL look identical. They have the same color blue caps and because the drug names appear vertically on the left margin of the label, it is impossible to tell them apart when the vials are partially turned. The boxes of ten that the products are packaged in also look alike.
7177109, 12/15/2010, 64 years old/female/89 kg, USA	Wrong dose	Unknown	Pt developed SOB, bronchospasm, copious secretions which were reversed with atropine.	Patient had subtotal gastrectomy. Post-op patient was to receive 1mg neostigmine, but RN gave 3mg in error.
4658270, 07/31/1997, Unknown/female/Unknown, USA	Wrong technique	Unknown	No harm	A physician requested Neostigmine "25 units: subq 4 times daily. The pharmacist told the doctor that neostigmine comes in a 1 mg/ml (1:1000) or 0.5 mg/mL (1:2000) solution. The doctor's patient insisted that she takes 25 units. The pharmacist then asked her to describe what the vial looks like, trying to confirm the strength she uses. The patient said that would be difficult for her to do since she is legally blind due to uncontrolled DM, but she knows what it feels like. So, the pharmacist handed her the 2 sizes of vials we carry and she identified the larger one (1mg/ml) as the strength she uses. The pharmacist then asked how she measures her dose. She told me that her home nurse pulls the plunger back to "35 units" and injects "25 units"). It was at that time that the pharmacist realized the nurse was using an insulin syringe to measure the dose, which was 0.25 mg (ie. " 25 units"). This really highlights the danger of using insulin syringe to measure doses for anything but insulin, as the physician could have easily ordered 25 mg of neostigmine. The patient could have received the wrong dose of the medication as well as a delay in treatment. A contributing factor would be using the incorrect syringe to draw up the medication.

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/s/

DENISE V BAUGH
05/25/2012

LUBNA A MERCHANT
05/25/2012

SCOTT M DALLAS
05/25/2012

CAROL A HOLQUIST
05/25/2012

REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

Application: 203629

Name of Drug: Neostigmine Methylsulfate Injection, USP

Applicant: APP Pharmaceuticals, LLC

Labeling Reviewed

Submission Date: December 29, 2011

Receipt Date: December 29, 2011

Background and Summary Description

Neostigmine Methylsulfate Injection is a marketed, unapproved product, indicated for reversal of nondepolarizing neuromuscular blocking agents. The SPL was submitted on January 20, 2012.

Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the “Selected Requirements for Prescribing Information (SRPI)” section of this review. Labeling deficiencies are identified in this section with an “X” in the checkbox next to the labeling requirement.

Conclusions/Recommendations

No deficiencies were identified in the review of this labeling.

Allison Meyer	3/8/12
Regulatory Project Manager	Date
Parinda Jani	3/13/12
Chief, Project Management Staff	Date

Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

• Highlights Limitation Statement (required statement)
• Drug names, dosage form, route of administration, and controlled substance symbol, if applicable (required information)
• Initial U.S. Approval (required information)
• Boxed Warning (if applicable)
• Recent Major Changes (for a supplement)
• Indications and Usage (required information)
• Dosage and Administration (required information)
• Dosage Forms and Strengths (required information)
• Contraindications (required heading - if no contraindications are known, it must state "None")
• Warnings and Precautions (required information)
• Adverse Reactions (required AR contact reporting statement)
• Drug Interactions (optional heading)
• Use in Specific Populations (optional heading)

<ul style="list-style-type: none">• Patient Counseling Information Statement (required statement)
<ul style="list-style-type: none">• Revision Date (required information)

- **Highlights Limitation Statement**

- Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

- **Product Title**

- Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**

- The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**

- All text in the boxed warning is **bolded**.
- Summary of the warning must not exceed a length of 20 lines.
- Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
- Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**

- Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
- The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) ~ 2/2010.”
- For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
- A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.

- Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) – removal 2/2010.”

- **Indications and Usage**
 - If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)).” Identify the established pharmacologic class for the drug at:
<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**
 - This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
 - All contraindications listed in the FPI must also be listed in HL.
 - List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
 - For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**
 - Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
 - For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**
 - Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”).**”

- **Revision Date**
 - A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers (not 8.2)
 - 8.4 Pediatric Use (not 8.3)
 - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI)

- **General Format**

- A horizontal line must separate the TOC and FPI.
- The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**

- Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
- Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**

- For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.
- For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”
- For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

- **Use in Specific Populations**

- Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

- This section is required and cannot be omitted.
- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:
 - “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

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/s/

ALLISON MEYER
03/14/2012

PARINDA JANI
03/14/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 203629 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Established/Proper Name: Neostigmine Methylsulfate Dosage Form: Injection Strengths: 0.5 mg/mL and 1.0 mg/mL		
Applicant: APP Pharmaceuticals, Inc. Agent for Applicant (if applicable):		
Date of Application: December 28, 2011 Date of Receipt: December 29, 2011 Date clock started after UN:		
PDUFA Goal Date: October 29, 2012	Action Goal Date (if different):	
Filing Date: February 27, 2012	Date of Filing Meeting: January 19, 2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3		
Proposed indication(s)/Proposed change(s): reversal of non-depolarizing neuromuscular blocking agents, 		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 106574				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	x			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	x			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	x			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		x		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	x			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>
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<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>
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505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		x		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		x		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i>		x		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm		x		

If yes, please list below:

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i>		x		

http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>			x	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>		x		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?		x		
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>			x	
Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) X CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	x			
Index: Does the submission contain an accurate comprehensive index?	x			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:	x			

¹
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?				
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	x			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	x			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	x			Form is located under cover letter section
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?		xx		All literature, no financial disclosure needed.
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	x			Form located under cover letter
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	x			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			x	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> Date of consult sent to Controlled Substance Staff:</p>			x	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	xx			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?		xx		Requested in 74-day letter
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>		xx		Requested in 74-day letter
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>			xx	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		xx		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>		x		
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the DCRMSRMP mailbox</i>		x		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	x			
Is the PI submitted in PLR format? ⁴	x			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	x			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)			x	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	x			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>		x		
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)?		x		

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

Date(s):				
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): December 22, 2009	x			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):		x		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 19, 2012

BLA/NDA/Supp #: 203629

PROPRIETARY NAME: TBD

ESTABLISHED/PROPER NAME: Neostigmine Methylsulfate

DOSAGE FORM/STRENGTH: Injection/0.5 mg/mL and 1.0 mg/mL

APPLICANT: APP Pharmaceuticals

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): reversal of non-depolarizing neuromuscular blocking agents. (b) (4)

BACKGROUND: Neostigmine is a marketed, unapproved drug. It has been submitted as a literature based 505(b)(2) NDA.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Allison Meyer	Y
	CPMS/TL:	Parinda Jani	N
Cross-Discipline Team Leader (CDTL)	Chris Breder		Y
Clinical	Reviewer:	Art Simone	Y
	TL:	Chris Breder	Y
Clinical Pharmacology	Reviewer:	David Lee	Y
	TL:	Yun Xu	Y
Biostatistics	Reviewer:	Jon Norton	N
	TL:	Dionne Price	Y
Nonclinical	Reviewer:	Huiqing Hao	Y

(Pharmacology/Toxicology)	TL:	Dan Mellon	Y
	Reviewer:	Edwin Jao	Y
Product Quality (CMC)	TL:	Prasad Peri	Y
	Reviewer:	Vinayak Pawar	N
Quality Microbiology (<i>for sterile products</i>)	TL:	John Metcalfe	N
	Reviewer:		
Facility Review/Inspection	TL:		
	Reviewer:		
OSE/DMEPA (proprietary name)	TL:		
	Reviewer:		
Other reviewers: Biopharmaceutics	Minerva Hughes		Y
Other attendees			

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input checked="" type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>Comments:</p> <ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

<p>If no, explain:</p>	
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<p><input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined</p> <p>Reason:</p>
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>BIOSTATISTICS</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p>

<p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Bob Rappaport or Rigoberto Roca

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	<p>The application is unsuitable for filing. Explain why:</p>
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>

ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
<input type="checkbox"/>	Other

Allison Meyer

2/27/12

Regulatory Project Manager

Date

Chief, Project Management Staff

Date

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

- (3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALLISON MEYER
03/07/2012

PARINDA JANI
03/07/2012