

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203629Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

**PATENT INFORMATION SUBMITTED WITH THE FILING  
OF AN NDA, AMENDMENT, OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance  
(Active Ingredient), Drug Product (Formulation and Composition)  
and/or Method of Use*

NDA NUMBER

203-629

NAME OF APPLICANT/NDA HOLDER

APP PHARMACEUTICALS LLC

*The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.*

TRADE NAME (OR PROPOSED TRADE NAME)

Neostigmine Methylsulfate Injection, USP

ACTIVE INGREDIENT(S)

Neostigmine Methylsulfate, USP

STRENGTH(S)

0.5 mg/mL and 1.0 mg/mL

DOSAGE FORM

(b) (4)

Injectable Liquid

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

**For hand-written or typewriter versions (only) of this report:** If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

**FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.**

**For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.**

**1. GENERAL**

a. United States Patent Number

b. Issue Date of Patent

c. Expiration Date of Patent

d. Name of Patent Owner

Address (of Patent Owner)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No

2.6 Does the patent claim only an intermediate?  Yes  No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No

3.2 Does the patent claim only an intermediate?  Yes  No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

**Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:**

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2 Patent Claim Number(s) (as listed in the patent) Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

**5. No Relevant Patents.**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

**6. Declaration Certification**

**6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.**

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

**6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)**

Date Signed



12/28/11

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

**Check applicable box and provide information below.**

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

James Harn

Address

1501 E Woodfield Rd., Suite 300 E.

City/State

Schaumburg, IL

ZIP Code

60173

Telephone Number

847-517-5767

FAX Number (if available)

847-413-8570

E-Mail Address (if available)

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The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services  
Food and Drug Administration  
Office of Chief Information Officer  
1350 Piccard Drive, Room 400  
Rockville, MD 20850

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*

1.3.5.1 Patent Information (Neostigmine Methylsulfate Injection, USP, 0.5 mg/mL and 1.0 mg/mL, (b)(4))

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1.3.5.1 Patent Certification and Exclusivity Statement (Neostigmine Methylsulfate Injection, USP, 0.5 mg/mL and 1.0 mg/mL, (b)(4))

1.3.5.1 Patent Information

The *Approved Drug Products with Therapeutic Equivalence Evaluations* (The Orange Book), obtained from the FDA website was reviewed for patent and exclusivities data for Neostigmine Methylsulfate Injection, USP. Neostigmine Methylsulfate Injection, USP is not listed in the electronic Orange Book and there are no unexpired patents or exclusivities for the product.

1.3.5.2 Patent Certification (Neostigmine Methylsulfate Injection, USP, 0.5 mg/mL and 1.0 mg/mL, (b)(4))

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**1.3.5 Patent Certification and Exclusivity Statement (Neostigmine Methylsulfate Injection, USP 0.5 mg/mL and 1.0 mg/mL, (b)(4))**

**1.3.5.2 Patent Certification**

There are no unexpired patents or exclusivities for Neostigmine Methylsulfate Injection, USP. Therefore, APP Pharmaceuticals, LLC (APP), a Company of the Fresenius Kabi Group, is not submitting Patent Certification and Exclusivity Statements for this 505 (b)(2) NDA submission. See attached PATENT CERTIFICATION AND EXCLUSIVITY STATEMENT.



**PATENT CERTIFICATION AND EXCLUSIVITY STATEMENT**

**Paragraph I Certification:**

APP Pharmaceuticals, LLC (APP), A Division of the Fresenius Kabi Group, hereby provides Patent Certification with respect to its New Drug Application (NDA), under Section 505(b)(2), for Neostigmine Methylsulfate Injection, USP. APP certifies that, in our opinion and to the best of our knowledge, patent information has not been filed with the FDA with respect to Neostigmine Methylsulfate Injection, USP for which APP seeks marketing clearance.

This certification is made in accordance with Section 505(j)(2)(A)(vii)(I) of Title I of the FD&C Act as amended September 24, 1984.

**Exclusivity Statement:**

APP Pharmaceuticals, LLC (APP) certifies that there are no exclusivity periods in effect with respect to the Neostigmine Methylsulfate Injection, USP drug product which has been referenced by APP in this ANDA.

As described elsewhere in this application, APP seeks marketing clearance for the following strength of Neostigmine Methylsulfate Injection, USP:

0.5 mg/mL, Product Code 38210, 10-mL fill in 10-cc vial  
1.0 mg/mL, Product Code 38310, 10-mL fill in 10-cc vial

APP Pharmaceuticals, LLC

By:

  
Dale Carlson, Senior Director  
Regulatory Affairs

Dec. 20, 2011

Date

APP Pharmaceuticals  
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Suite 300 East  
Schaumburg, IL 60173  
Main 847-969-2700  
Toll Free 888-391-6300  
www.APPpharma.com

## EXCLUSIVITY SUMMARY

NDA # 203629

HFD # 170

Trade Name: Not Available

Generic Name: neostigmine methylsulfate injection

Applicant Name: Fresenius Kabi USA LLC

Approval Date, If Known: January 8, 2015

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

b) If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

The submission contains only published literature to support the indication. The Applicant did not conduct any clinical studies to support the safety and efficacy of this product.

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

This product is labeled for use in all relevant pediatric populations. Therefore, no additional pediatric studies are needed.

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

### 1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

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YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 000654 Prostigmin (neostigmine bromide)

NDA# 204078 Bloxiverz

NDA#

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed

only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation

NDA 203629

duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !  
IND # YES  ! NO   
! Explain:

Investigation #2 !  
IND # YES  ! NO   
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was

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not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !  
! YES  NO   
Explain: ! Explain:

Investigation #2 !  
! YES  NO   
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES  NO

If yes, explain:



Name of person completing form: Allison Meyer  
Title: Regulatory Health Project Manager  
Date: January 6, 2015

Name of Office/Division Director signing form: Rigoberto Roca, Deputy Director  
Title: Director, HFD-170

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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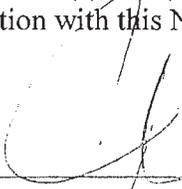
ALLISON MEYER  
01/08/2015

RIGOBERTO A ROCA  
01/08/2015

APP

**DEBARMENT CERTIFICATION**

In compliance with the requirements of the Generic Drug Enforcement Act of 1992, Subsections (a) and (b) of Section 306, APP Pharmaceuticals, LLC hereby certifies that it did not and will not use in any capacity the services of any person debarred under Subsections (a) and (b) of Section 335a of the Federal Food, Drug, and Cosmetic Act in connection with this NDA for Neostigmine Methylsulfate Injection, USP.



James Callanan, Vice President  
Human Resources

8-2-11

Date

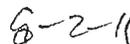
APP Pharmaceuticals | Main 847-969-2700  
1501 East Woodfield Road | Toll Free 888-391-6300  
Suite 300 East | www.APPpharma.com  
Schaumburg, IL 60173

CONVICTIONS LISTING CERTIFICATION

APP Pharmaceuticals, LLC hereby certifies that it has not been convicted within the last five years of any crimes described in Subsections (a) and (b) of Section 335a of the Federal Food, Drug, and Cosmetic Act. In compliance with the requirements of the Generic Drug Enforcement Act of 1992, Subsections (a) and (b) of Section 306, APP Pharmaceuticals, LLC hereby certifies that it has not used in any capacity the services of any person who has been convicted within the last five years of any crimes described in Subsections (a) and (b) of Section 335a of the Federal Food, Drug, and Cosmetic Act in connection with this NDA for Neostigmine Methylsulfate Injection, USP. Therefore, APP Pharmaceuticals, LLC has no convictions to list.



James Callahan, Vice President  
Human Resources



Date

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 203629 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Established/Proper Name: Neostigmine Methylsulfate Dosage Form: Injection		Applicant: Fresenius Kabi USA LLC Agent for Applicant (if applicable):
RPM: Allison Meyer		Division: Anesthesia, Analgesia, and Addiction Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)	<p style="margin: 0;"><b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b></p> <ul style="list-style-type: none"> <li>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</li> <li>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul> <p style="margin: 5px 0 0 20px;"> <input checked="" type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>)            Date of check:         </p> <p style="margin: 5px 0 0 20px;"><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>	
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>January 9, 2015</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input type="checkbox"/> None    CR 1/29/13
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority:  Standard  Priority  
 Chemical classification (new NDAs only):  
*(confirm chemical classification at time of approval)*

- |   |   |
|---|---|
| <input type="checkbox"/> Fast Track                       | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input type="checkbox"/> Rolling Review                   | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input type="checkbox"/> Breakthrough Therapy designation |   |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)  
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR  
 Submitted in response to a PMC  
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)  
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS:  MedGuide  
 Communication Plan  
 ETASU  
 MedGuide w/o REMS  
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 <i>(approvals only)</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications <i>(approvals only)</i>	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list <i>(approvals only)</i>	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters (including approval letter with final labeling)	Action(s) and date(s) 1/8/15 AP, 1/29/13 CR
Labeling	
❖ Package Insert (write submission/communication date at upper right of first page of PI)	
<ul style="list-style-type: none"> <li>Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)</li> </ul>	<input type="checkbox"/> Included
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<input type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
<ul style="list-style-type: none"> <li>Most-recent draft labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	N/A
<ul style="list-style-type: none"> <li>Acceptability/non-acceptability letter(s) (indicate date(s))</li> <li>Review(s) (indicate date(s))</li> </ul>	
❖ Labeling reviews (indicate dates of reviews)	RPM: <input type="checkbox"/> None 3/14/12 DMEPA: <input type="checkbox"/> None 1/2/15, 12/16/14, 5/25/12 DMPP/PLT (DRISK): <input checked="" type="checkbox"/> None OPDP: <input type="checkbox"/> None 12/31/14, 1/14/13 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting (indicate date of each review)	3/7/12
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input type="checkbox"/> Not a (b)(2) 12/9/14, 12/17/12
❖ NDAs only: Exclusivity Summary (signed by Division Director)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> <li>This application is on the AIP                             <ul style="list-style-type: none"> <li>If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>Date reviewed by PeRC <u>12/5/12</u> If PeRC review not necessary, explain: _____</li> </ul>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) ( <i>do not include previous action letters, as these are located elsewhere in package</i> )	1/8/15, 1/7/15, 12/18/14, 12/16/14, 10/7/14, 7/23/14, 1/28/13, 10/18/12, 10/17/12, 10/4/12, 10/3/12, 9/20/12, 8/29/12, 8/22/12, 7/12/12, 6/22/12, 5/29/12, 5/24/12, 4/23/12, 3/28/12, 3/19/12, 3/12/12, 1/18/12
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> <li>If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> <li>Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg   12/22/09
<ul style="list-style-type: none"> <li>EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)</li> </ul>	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>Date(s) of Meeting(s)</li> </ul>	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None   1/8/15, 1/29/13
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None   1/6/13
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input type="checkbox"/> None   1/8/15
<b>Clinical</b>	
❖ Clinical Reviews	
<ul style="list-style-type: none"> <li>Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> <li>Clinical review(s) (<i>indicate date for each review</i>)</li> </ul>	12/16/14, 9/18/12
<ul style="list-style-type: none"> <li>Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input checked="" type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	9/18/12
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None

❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	<input checked="" type="checkbox"/> None requested
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 9/4/12
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 12/23/14, 8/24/12, 2/22/12
❖ OSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review 9/18/12
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 12/17/14, 8/28/12, 1/25/12
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested

<b>Product Quality</b> <input type="checkbox"/> None	
<b>❖ Product Quality Discipline Reviews</b>	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 12/22/14, 12/3/14, 1/29/12, 12/21/12, 9/20/12
<b>❖ Microbiology Reviews</b> <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input type="checkbox"/> Not needed 9/10/12, 2/22/12
<b>❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer</b> <i>(indicate date of each review) Biopharmaceutics</i>	<input type="checkbox"/> None 12/3/14, 8/23/12, 2/8/12
<b>❖ Environmental Assessment (check one) (original and supplemental applications)</b>	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	9/20/12
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
<b>❖ Facilities Review/Inspection</b>	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do <b>NOT</b> include EER Detailed Report; date completed must be within <b>2 years</b> of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>5</sup>)</i>	Date completed: 12/22/14, 1/28/12 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within <b>30 days</b> of action date) <i>(original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<b>❖ NDAs: Methods Validation</b> <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

<sup>5</sup> i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul>	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
<ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul>	<input checked="" type="checkbox"/> Done
❖ For Breakthrough Therapy(BT) Designated drugs: <ul style="list-style-type: none"> <li>• Notify the CDER BT Program Manager</li> </ul>	<input type="checkbox"/> Done ( <i>Send email to CDER OND IO</i> )
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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/s/  
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ALLISON MEYER  
01/14/2015

## Meyer, Allison

---

**From:** Meyer, Allison  
**Sent:** Thursday, January 08, 2015 1:32 PM  
**To:** 'Grace.Burbulys@fresenius-kabi.com'  
**Cc:** Brad.Schmitt@fresenius-kabi.com; Molly.Rapp@fresenius-kabi.com  
**Subject:** RE: NDA 203629 package insert labeling  
**Attachments:** NDA 203629 package insert 07 Jan 2015.doc

Grace/Molly/Brad,

Please see a few minor changes. If this is ok, I will accept changes and use this as the final version of the package insert. Please respond ASAP.

Allison

**From:** Grace.Burbulys@fresenius-kabi.com [mailto:Grace.Burbulys@fresenius-kabi.com]  
**Sent:** Thursday, January 08, 2015 11:30 AM  
**To:** Meyer, Allison  
**Cc:** Brad.Schmitt@fresenius-kabi.com; Molly.Rapp@fresenius-kabi.com  
**Subject:** RE: NDA 203629 package insert labeling

Good morning Allison,

Yes, we verified all the cross-references.

Best regards,

Grace

Grace Burbulys  
Sr.Regulatory Specialist  
Fresenius Kabi USA, LLC  
Three Corporate Drive  
Lake Zurich, IL 60047  
email: [grace.burbulys@fresenius-kabi.com](mailto:grace.burbulys@fresenius-kabi.com)  
T: +1 847-550-2684  
F: +1 847-550-7120

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From: "Meyer, Allison" <[Allison.Meyer@fda.hhs.gov](mailto:Allison.Meyer@fda.hhs.gov)>  
To: "[Grace.Burbulys@fresenius-kabi.com](mailto:Grace.Burbulys@fresenius-kabi.com)" <[Grace.Burbulys@fresenius-kabi.com](mailto:Grace.Burbulys@fresenius-kabi.com)>,  
Cc: "[Molly.Rapp@fresenius-kabi.com](mailto:Molly.Rapp@fresenius-kabi.com)" <[Molly.Rapp@fresenius-kabi.com](mailto:Molly.Rapp@fresenius-kabi.com)>, "[Brad.Schmitt@fresenius-kabi.com](mailto:Brad.Schmitt@fresenius-kabi.com)" <[Brad.Schmitt@fresenius-kabi.com](mailto:Brad.Schmitt@fresenius-kabi.com)>  
Date: 01/08/2015 10:21 AM  
Subject: RE: NDA 203629 package insert labeling

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Are all the cross-references verified?

**From:** [Grace.Burbulys@fresenius-kabi.com](mailto:Grace.Burbulys@fresenius-kabi.com) [<mailto:Grace.Burbulys@fresenius-kabi.com>]  
**Sent:** Wednesday, January 07, 2015 5:04 PM  
**To:** Meyer, Allison  
**Cc:** [Molly.Rapp@fresenius-kabi.com](mailto:Molly.Rapp@fresenius-kabi.com); [Brad.Schmitt@fresenius-kabi.com](mailto:Brad.Schmitt@fresenius-kabi.com)  
**Subject:** Re: NDA 203629 package insert labeling

Hi Allison,

We agree with the Agency's changes to the package insert for NDA 203629 . We hereby submit the package insert in Word and pdf formats per your recommendations in the 06 Jan 2015 email below .

Please contact us if you have any questions.

Best regards,

Grace

Grace Burbulys  
Sr.Regulatory Specialist  
Fresenius Kabi USA, LLC  
Three Corporate Drive  
Lake Zurich, IL 60047  
email: [grace.burbulys@fresenius-kabi.com](mailto:grace.burbulys@fresenius-kabi.com)  
T: +1 847-550-2684  
F: +1 847-550-7120

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From: "Meyer, Allison" <[Allison.Meyer@fda.hhs.gov](mailto:Allison.Meyer@fda.hhs.gov)>  
To: "[Molly.Rapp@fresenius-kabi.com](mailto:Molly.Rapp@fresenius-kabi.com)" <[Molly.Rapp@fresenius-kabi.com](mailto:Molly.Rapp@fresenius-kabi.com)>, "[Grace.Burbulys@fresenius-kabi.com](mailto:Grace.Burbulys@fresenius-kabi.com)" <[Grace.Burbulys@fresenius-kabi.com](mailto:Grace.Burbulys@fresenius-kabi.com)>,  
Date: 01/06/2015 06:26 PM  
Subject: package insert labeling

---

Molly/Grace,

Attached are the marked up and clean versions of the package insert from the Division. Please let us know by 2 pm (Eastern time) tomorrow, 1/7/15, if you have any comments.

1. Fix the margins to ½" as required by the PLR Guidance. Currently, the HIGHLIGHTS is 1" and TOC and FPI are 1 ½". This is necessary for the web posting.
2. Verify and add all the cross-references.

Allison Meyer  
Sr. Regulatory Health Project Manager  
Division of Anesthesia, Analgesia and

Addiction Products  
Office of New Drugs II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Bldg. 22, Rm. 3176  
Silver Spring, MD 20993  
301-796-1258  
301-796-9713 (fax)

[attachment "clean pi 1 6.doc" deleted by Grace Burbulys/RA/SC/US/HHC/Fresenius] [attachment "pdf label with edits 1 6.pdf" deleted by Grace Burbulys/RA/SC/US/HHC/Fresenius]

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/s/  
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ALLISON MEYER  
01/08/2015

## Meyer, Allison

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**From:** Meyer, Allison  
**Sent:** Thursday, December 18, 2014 10:24 AM  
**To:** Molly.Rapp@fresenius-kabi.com; Brad.Schmitt@fresenius-kabi.com  
**Cc:** Grace.Burbulys@fresenius-kabi.com  
**Subject:** NDA 203629 labeling IR

Molly,

The following comments will need to be addressed by 12/22/14:

### 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.<sup>5</sup>
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.<sup>5</sup>
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.
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.

Allison Meyer  
Sr. Regulatory Health Project Manager  
Division of Anesthesia, Analgesia and  
Addiction Products  
Office of New Drugs II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Bldg. 22, Rm. 3176  
Silver Spring, MD 20993

301-796-1258  
301-796-9713 (fax)

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/s/  
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ALLISON MEYER  
12/18/2014

## **Meyer, Allison**

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**From:** Meyer, Allison  
**Sent:** Tuesday, December 16, 2014 9:53 AM  
**To:** Molly.Rapp@fresenius-kabi.com  
**Cc:** Grace.Burbulys@fresenius-kabi.com  
**Subject:** NDA 203629 IR

Submit the rat and rabbit pilot dose range-finding study reports (Protocols 1999-004 and 1999-005) via email and follow up with a formal submission to your NDA 203629.

This submission is needed by December 19, 2014.

Allison Meyer  
Sr. Regulatory Health Project Manager  
Division of Anesthesia, Analgesia and  
Addiction Products  
Office of New Drugs II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Bldg. 22, Rm. 3176  
Silver Spring, MD 20993  
301-796-1258  
301-796-9713 (fax)

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/s/  
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ALLISON MEYER  
12/16/2014

## **Meyer, Allison**

---

**From:** Meyer, Allison  
**Sent:** Tuesday, October 07, 2014 9:33 AM  
**To:** Grace.Burbulys@fresenius-kabi.com  
**Subject:** information request Neostigmine

Grace,

We are inquiring as to whether you have received adverse event reports for Lack of Efficacy for neostigmine.

We are interested in:

- the number of report counts per month for the event of Lack of Efficacy that you have received since approval of their product.
- a summary of your review of potential underlying factors.
- a copy of the adverse event reports.

We would like to receive the submission by October 17.

Allison Meyer  
Sr. Regulatory Health Project Manager  
Division of Anesthesia, Analgesia and  
Addiction Products  
Office of New Drugs II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Bldg. 22, Rm. 3176  
Silver Spring, MD 20993  
301-796-1258  
301-796-9713 (fax)

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/s/  
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ALLISON MEYER  
10/08/2014



NDA 203629

**ACKNOWLEDGE –  
CLASS 2 RESUBMISSION**

Fresenius Kabi USA, LLC  
1501 E. Woodfield Road, Suite 300 East  
Schaumburg, IL 60173

Attention: Dale Carlson  
Senior Director, Regulatory Affairs

Dear Mr. Carlson:

We acknowledge receipt on July 11, 2014, of your July 11, 2014, resubmission to your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Neostigmine Methylsulfate Injection, USP.

We consider this a complete, class 2 response to our January 29, 2013 action letter. Therefore, the user fee goal date is January 11, 2015.

If you have any questions, call me, at (301) 796-1258.

Sincerely,

*{See appended electronic signature page}*

Allison Meyer  
Sr. Regulatory Health Project Manager  
Division of Anesthesia, Analgesia,  
and Addiction Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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ALLISON MEYER  
07/23/2014

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 203629 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Established/Proper Name: Neostigmine Methylsulfate Dosage Form: Injection		Applicant: Fresenius Kabi USA, LLC. Agent for Applicant (if applicable):
RPM: Allison Meyer		Division: Anesthesia, Analgesia and Addiction Products
<p><b><u>NDA and NDA Efficacy Supplements:</u></b></p> <p>NDA Application Type:    <input type="checkbox"/> 505(b)(1)    <input checked="" type="checkbox"/> 505(b)(2)            Efficacy Supplement:    <input type="checkbox"/> 505(b)(1)    <input type="checkbox"/> 505(b)(2)</p> <p>(A 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). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>	<p><b><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></b></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):            NDA 000654 Prostigmine</p> <p>Provide a brief explanation of how this product is different from the listed drug.            Prostigmine is an ophthalmic solution.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug.  <input checked="" type="checkbox"/> This application relies on literature.  <input type="checkbox"/> This application relies on a final OTC monograph.  <input type="checkbox"/> This application relies on (explain)</p> <p><b><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input type="checkbox"/> No changes    <input type="checkbox"/> Updated    Date of check:</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p>	
❖ Actions		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>January 29, 2013</u></li> </ul>	<input type="checkbox"/> AP <input type="checkbox"/> TA <input checked="" type="checkbox"/> CR	
<ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>	<input checked="" type="checkbox"/> None	

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?                  Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a>). If not submitted, explain _____</p>	<p><input type="checkbox"/> Received</p>
<p>❖ Application Characteristics<sup>3</sup></p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority                  Chemical classification (new NDAs only): 7 (marketed unapproved)</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch  <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC             </p> <p>                 NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510)  <input type="checkbox"/> Restricted distribution (21 CFR 314.520)                  Subpart I <input type="checkbox"/> Approval based on animal studies             </p> <p> <input type="checkbox"/> Submitted in response to a PMR  <input type="checkbox"/> Submitted in response to a PMC  <input type="checkbox"/> Submitted in response to a Pediatric Written Request             </p> <p>                 BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41)  <input type="checkbox"/> Restricted distribution (21 CFR 601.42)                  Subpart H <input type="checkbox"/> Approval based on animal studies             </p> <p>                 REMS: <input type="checkbox"/> MedGuide  <input type="checkbox"/> Communication Plan  <input type="checkbox"/> ETASU  <input type="checkbox"/> MedGuide w/o REMS  <input checked="" type="checkbox"/> REMS not required             </p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<p><input type="checkbox"/> Yes, dates</p>
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> <li>Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> <li>Press Office notified of action (by OEP)</li> </ul>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<p> <input type="checkbox"/> None  <input type="checkbox"/> HHS Press Release  <input type="checkbox"/> FDA Talk Paper  <input type="checkbox"/> CDER Q&amp;As  <input type="checkbox"/> Other             </p>

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes     No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

*If "Yes," skip to question (4) below. If "No," continue with question (2).*

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes     No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

*If "No," continue with question (3).*

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes     No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

*If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes     No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).*

*If "No," continue with question (5).*

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
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**CONTENTS OF ACTION PACKAGE**

❖ Copy of this Action Package Checklist <sup>4</sup>	1/29/13
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input type="checkbox"/> Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) 1/29/13 CR
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	1/28/13
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	12/29/11
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	

<sup>4</sup> Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> <li>❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)</li> </ul>	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Labels (<b>full color</b> carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	12/29/11
<ul style="list-style-type: none"> <li>❖ Proprietary Name             <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> <li>• Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</li> </ul> </li> </ul>	N/A
<ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input checked="" type="checkbox"/> RPM 3/14/12 <input checked="" type="checkbox"/> DMEPA 5/25/12 <input type="checkbox"/> DMPP/PLT (DRISK) <input checked="" type="checkbox"/> ODPD (DDMAC) 1/14/13 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<b>Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>❖ Administrative Reviews (<i>e.g., RPM Filing Review<sup>5</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> </ul>	3/7/12
<ul style="list-style-type: none"> <li>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</li> </ul>	<input type="checkbox"/> Not a (b)(2) 12/17/12
<ul style="list-style-type: none"> <li>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</li> </ul>	<input type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<input type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents  <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a> </li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP             <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>)             <ul style="list-style-type: none"> <li>• Date reviewed by PeRC _____ If PeRC review not necessary, explain: _____</li> <li>• Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)</li> </ul>	<input checked="" type="checkbox"/> Verified, statement is acceptable

<sup>5</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Outgoing communications ( <i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i> )	10/18/12, 10/17/12, 10/4/12, 10/3/12, 9/20/12, 8/29/12, 8/22/12, 7/12/12, 6/22/12, 5/29/12, 5/24/12, 4/23/12, 3/28/12, 3/19/12, 3/12/12, 1/18/12
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg 12/22/09
• EOP2 meeting ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) ( <i>indicate dates of mtgs</i> )	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available ( <i>do not include transcript</i> )	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 1/29/13
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 1/6/13
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None
<b>Clinical Information<sup>6</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	
• Clinical review(s) ( <i>indicate date for each review</i> )	9/18/12
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input checked="" type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	9/18/12
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management	
• REMS Documents and Supporting Statement ( <i>indicate date(s) of submission(s)</i> )	
• REMS Memo(s) and letter(s) ( <i>indicate date(s)</i> )	
• Risk management review(s) and recommendations (including those by OSE and CSS) ( <i>indicate date of each review and indicate location/date if incorporated into another review</i> )	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	<input checked="" type="checkbox"/> None requested

<sup>6</sup> Filing reviews should be filed with the discipline reviews.

<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Statistical Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 9/4/12
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 8/24/12, 2/22/12
❖ DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 9/18/12
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 8/28/12, 1/25/12
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 1/29/12, 12/21/12, 9/20/12
❖ Microbiology Reviews	<input type="checkbox"/> Not needed 9/10/12, 2/22/12
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review) Biopharmaceutics</i>	<input type="checkbox"/> None 8/23/12, 2/8/12

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	9/20/12
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) ( <i>date completed must be within 2 years of action date</i> ) ( <i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>7</sup></i> )	Date completed: 1/28/12 <input type="checkbox"/> Acceptable <input checked="" type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER ( <i>date of most recent TB-EER must be within 30 days of action date</i> ) ( <i>original and supplemental BLAs</i> )	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation ( <i>check box only, do not include documents</i> )	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

<sup>7</sup> I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

## Appendix to Action Package Checklist

An NDA or NDA supplemental 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) **Or** 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.
- (3) **Or** 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) **And** 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.
- (3) **And** 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) **Or** 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.
- (3) **Or** 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 ODE's ADRA.

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

ALLISON MEYER  
01/31/2013

## Meyer, Allison

---

**From:** Meyer, Allison  
**Sent:** Wednesday, January 18, 2012 10:14 AM  
**To:** James.Harn@fresenius-kabi.com  
**Subject:** RE: Neostigmine

James,  
SPL is a requirement for filing. We will need your SPL by the filing date.  
Allison

---

**From:** James.Harn@fresenius-kabi.com [mailto:James.Harn@fresenius-kabi.com]  
**Sent:** Friday, January 13, 2012 2:33 PM  
**To:** Meyer, Allison  
**Subject:** Re: Neostigmine

Confirmed.

Looking forward to hearing the result of SPL submission requirements.

### James Harn

Fresenius Kabi USA  
1501 East Woodfield Road Suite 300 East  
Schaumburg, Illinois 60173  
T: +1 847-517-5767  
[James.Harn@fresenius-kabi.com](mailto:James.Harn@fresenius-kabi.com)  
[www.fresenius-kabi.us](http://www.fresenius-kabi.us)

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**From:** "Meyer, Allison" <Allison.Meyer@fda.hhs.gov>  
**To:** "James.Harn@fresenius-kabi.com" <james.harn@fresenius-kabi.com>  
**Date:** 01/13/2012 01:29 PM  
**Subject:** Neostigmine

---

Confirmation of email address.

Allison Meyer

Sr. Regulatory Health Project Manager  
Division of Anesthesia, Analgesia and  
Addiction Products  
Office of New Drugs II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Bldg. 22, Rm. 3176  
Silver Spring, MD 20993  
301-796-1258  
301-796-9713 (fax)

**Meyer, Allison**

---

**From:** Meyer, Allison  
**Sent:** Wednesday, August 22, 2012 2:30 PM  
**To:** 'James.Harn@fresenius-kabi.com'  
**Subject:** Neostigmine

How long have **you** been marketing the formulation that **you** are seeking to have approved and approximately how many vials of that formulation have been sold?

Thanks.

Allison Meyer  
Sr. Regulatory Health Project Manager  
Division of Anesthesia, Analgesia and  
Addiction Products  
Office of New Drugs II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Bldg. 22, Rm. 3176  
Silver Spring, MD 20993  
301-796-1258  
301-796-9713 (fax)

## Meyer, Allison

---

**From:** Meyer, Allison  
**Sent:** Tuesday, May 29, 2012 2:23 PM  
**To:** 'James.Harn@fresenius-kabi.com'  
**Subject:** IR for APP neostigmine NDA

Please respond by Monday, June 4th.

The Dosing and Administration section of the proposed label does not provide the information needed by clinicians to select an appropriate dose of neostigmine for a given patient and to administer the drug product in a safe and effective manner. Specifically, the labeling needs to be revised to indicate the following:

- when it is appropriate to administer neostigmine (e.g., time since last dose of NMBA, return of a certain percentage of a twitch response, return of a certain ratio of the TOF stimulus response)
- in what clinical settings should the neostigmine dose be at the lower end of the dosing range and when it should be at the upper end
- how to determine whether the dose of neostigmine adequately reversed the effects of the NMBA
- the length of time that must pass after administration of a dose of neostigmine to determine whether the dose was adequate or additional product should be given to effectively reverse the actions of the NMBA

Provide a summary of the literature published since the cutoff for your previous review and indicate whether the newer literature raises any new safety concerns or provides data that would allow refinement of the proposed methods of use.

We note that some literature pertinent to the NDA and published in the time range for your previous search was not included in the NDA submission, (e.g., Stefan J. Schaller, Heidrun Fink, Kurt Ulm, and Manfred Blobner: Sugammadex and Neostigmine Dose-finding Study for Reversal of Shallow Residual Neuromuscular Block. *Anesthesiology*, V 113 • No 5 • November 2010 p. 1054-60). Perform a search of the literature from the past 10 years looking for studies involving neostigmine in which different doses of the product or a placebo was used as a comparator for either safety or efficacy, and if necessary, update the safety or efficacy information in the NDA.

You have provided information on the pediatric use of neostigmine in patients from 0-17 years of age. At this time, a request for waiver or deferral is not needed. If the information provided for this patient population is found, on review, inadequate to make an assessment of safety, efficacy and appropriate dosing, we will request the necessary information to complete the review.

Thanks.

Allison Meyer  
Sr. Regulatory Health Project Manager  
Division of Anesthesia, Analgesia and  
Addiction Products  
Office of New Drugs II  
Center for Drug Evaluation and Research

10903 New Hampshire Avenue  
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Silver Spring, MD 20993  
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301-796-9713 (fax)

**Meyer, Allison**

---

**From:** Meyer, Allison  
**Sent:** Thursday, May 24, 2012 2:39 PM  
**To:** 'James.Harn@fresenius-kabi.com'  
**Subject:** information request

Jim, Please respond ASAP.

Although the concentration of phenol in your drug product appears to be lower than the concentration of phenol in other FDA-approved intravenous drug products, the maximum daily exposure to phenol following use of your drug product ( (b) (4) mg of phenol) appears to exceed that which would be administered via other FDA-approved intravenous drug products that contain phenol as a preservative. Therefore, reliance on the Agency's previous finding of safety for numerous IV drug products containing phenol at (b) (4)% is adequate to address the concern for the local tissue concentration of phenol in the drug product, however, it does not appear to address the concern for the total daily intravenous dose of phenol in your drug product or for the potential of local tissue toxicity of the drug product formulation. The safety of the drug product formulation in terms of local tissue irritation and potential formation of thrombi must be addressed in your NDA, either by reference to existing clinical experience with a comparable drug product, via toxicological data, or via a weight of evidence justification based on literature and/or other data. Submit a toxicological risk assessment for acute intravenous infusion of up to (b) (4) mg of phenol as a bolus injection. The risk assessment should address both the systemic toxicity of phenol and the potential for local tissue toxicity of your drug product formulation containing the proposed level of phenol.

Allison Meyer  
Sr. Regulatory Health Project Manager  
Division of Anesthesia, Analgesia and  
Addiction Products  
Office of New Drugs II  
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10903 New Hampshire Avenue  
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Silver Spring, MD 20993  
301-796-1258  
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## Meyer, Allison

---

**From:** Meyer, Allison  
**Sent:** Monday, April 23, 2012 9:28 AM  
**To:** 'James.Harn@fresenius-kabi.com'  
**Subject:** FW: Neostigmine NDA Impurity QSAR

**Attachments:** Neostigmine and Impurities QSAR Report FDA\_NDA203629.pdf



Neostigmine and  
Impurities QSA...

Allison Meyer  
Sr. Regulatory Health Project Manager  
Division of Anesthesia, Analgesia and  
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301-796-1258  
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## Meyer, Allison

---

**From:** Meyer, Allison  
**Sent:** Wednesday, March 28, 2012 8:57 AM  
**To:** 'James.Harn@fresenius-kabi.com'  
**Subject:** IR for neostigmine

James,  
The following request requires a response within 1 week:

Sort the clinical evidence of efficacy for neostigmine by the neuromuscular blocking agent(s) (NMBA) evaluated and then, for each NMBA, create a table with the following information:

1. Optimum time for neostigmine administration (e.g., time after last dose of NMBA, including the extent of TOF or T<sub>1</sub> recovery).
2. Optimum dose of neostigmine
  - a. For pediatric patients
  - b. For adult patients
  - c. For geriatric patients
3. Time frame following neostigmine administration during which recovery should be complete.

Include the following as an addendum to your information:

1. the range of times after the last dose of NMBA for administration of neostigmine that have been evaluated.
2. the doses of neostigmine that were evaluated for each patient subpopulation in Bullet 2
3. the range of time for which efficacy of neostigmine was evaluated following its administration

Also, identify the article(s) used to make each determination, for these requests.

Allison Meyer  
Sr. Regulatory Health Project Manager  
Division of Anesthesia, Analgesia and  
Addiction Products  
Office of New Drugs II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Bldg. 22, Rm. 3176  
Silver Spring, MD 20993  
301-796-1258  
301-796-9713 (fax)

## **Meyer, Allison**

---

**From:** Meyer, Allison  
**Sent:** Monday, March 19, 2012 1:24 PM  
**To:** 'James.Harn@fresenius-kabi.com'  
**Subject:** FW: Another IR

James,

Provide the documentation of the efforts you made to secure original protocols and data.

Thanks.

Allison Meyer  
Sr. Regulatory Health Project Manager  
Division of Anesthesia, Analgesia and  
Addiction Products  
Office of New Drugs II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Bldg. 22, Rm. 3176  
Silver Spring, MD 20993  
301-796-1258  
301-796-9713 (fax)

## Meyer, Allison

---

**From:** Meyer, Allison  
**Sent:** Monday, March 19, 2012 9:25 AM  
**To:** 'James.Harn@fresenius-kabi.com'  
**Subject:** FW: IR for APP regarding neostigmine

James,  
Please respond by COB Wednesday.

Identify the search criteria and the methods used to identify the articles from the literature that were included in the NDA.  
Identify the time period covered by the literature search.

Thanks.

Allison Meyer  
Sr. Regulatory Health Project Manager  
Division of Anesthesia, Analgesia and  
Addiction Products  
Office of New Drugs II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
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/s/  
-----

ALLISON MEYER  
01/28/2013

## Meyer, Allison

---

**From:** Meyer, Allison  
**Sent:** Thursday, October 04, 2012 9:46 AM  
**To:** Aditi.Dron@fresenius-kabi.com  
**Subject:** Clock extension

**Attachments:** Review Extension.pdf



Review  
xtension.pdf (22 KB)

Allison Meyer

Sr. Regulatory Health Project Manager  
Division of Anesthesia, Analgesia and  
Addiction Products  
Office of New Drugs II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
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Silver Spring, MD 20993  
301-796-1258  
301-796-9713 (fax)

## Meyer, Allison

---

**From:** Meyer, Allison  
**Sent:** Thursday, September 20, 2012 3:45 PM  
**To:** Aditi.Dron@fresenius-kabi.com  
**Subject:** RE: Neostigmine NDA 203629 - Facility Update

Aditi,  
Would you be able to give me a more precise date as to when your facility will be ready for re-inspection?  
Thank you,  
Allison

---

**From:** Aditi.Dron@fresenius-kabi.com [mailto:Aditi.Dron@fresenius-kabi.com]  
**Sent:** Wednesday, September 05, 2012 3:26 PM  
**To:** Rivera, Luz E (CDER); Meyer, Allison  
**Subject:** Neostigmine NDA 203629 - Facility Update

Dear Ms. Rivera, Ms. Meyer,

I am providing the following update regarding our Grand Island, NY manufacturing facility as requested by the Agency during the teleconference held on August 31, 2012 for our pending NDA 203629 for Neostigmine Methylsulfate Injection, USP.

The Grand Island, NY facility received a warning letter on February 22, 2012. All corrective actions will be complete by

the end of this year. Senior Management from our company had a meeting with the NY District Office and the Office of Compliance on August 24, 2012. The meeting was to update the FDA on the status of our corrective actions. We are expecting the Agency to perform a follow-up inspection soon but have no date.

Please feel free to contact me in case there are questions or comments regarding this information.

Sincerely,

Aditi Dron  
Regulatory Affairs Manager  
Fresenius Kabi USA, LLC

Phone: 847-330-3898  
Fax: 847-413-8570  
Email: aditi.dron@fresenius-kabi.com

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## Meyer, Allison

---

**From:** Meyer, Allison  
**Sent:** Wednesday, October 17, 2012 3:04 PM  
**To:** 'Aditi.Dron@fresenius-kabi.com'  
**Subject:** RE: teleconference for Neostigmine

[Do you intend to submit a proprietary name request for this drug?](#)  
Allison

---

**From:** Aditi.Dron@fresenius-kabi.com [mailto:Aditi.Dron@fresenius-kabi.com]  
**Sent:** Tuesday, October 16, 2012 9:20 AM  
**To:** Meyer, Allison  
**Subject:** Fw: teleconference for Neostigmine

Good Morning Ms. Meyer,

This is regarding the teleconference that the Agency has requested for this Thursday, October 18th for our Neostigmine NDA 203629. Can you let us know the broad topic of the discussion in addition to 'clinical and non-clinical' so that we can have the appropriate personnel available at the teleconference.

Thank you,

Aditi Dron  
Regulatory Affairs Manager  
Fresenius Kabi USA, LLC

Phone: 847-330-3898  
Fax: 847-413-8570  
Email: aditi.dron@fresenius-kabi.com

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----- Forwarded by Aditi Dron/RA/SC/US/HHC/Fresenius on 10/16/2012 08:15 AM -----

From: Aditi Dron/RA/SC/US/HHC/Fresenius  
To: "Meyer, Allison" <Allison.Meyer@fda.hhs.gov>  
Date: 10/08/2012 04:34 PM  
Subject: Re: teleconference for Neostigmine

---

Dear Ms. Meyer,

I am providing the call in number for the teleconference to be held on October 18th, 2012 at 3:30 PM (eastern time):

Dial In Number: (b) (4)  
Conference Code: (b) (4)

Sincerely,

Aditi Dron  
Regulatory Affairs Manager  
Fresenius Kabi USA, LLC

Phone: 847-330-3898  
Fax: 847-413-8570  
Email: aditi.dron@fresenius-kabi.com

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From: "Meyer, Allison" <Allison.Meyer@fda.hhs.gov>  
To: "Aditi.Dron@fresenius-kabi.com" <Aditi.Dron@fresenius-kabi.com>  
Date: 10/05/2012 01:04 PM  
Subject: teleconference for Neostigmine

Aditi,  
We need to have a teleconference on October 18th at 3:30 pm (eastern time) to discuss some post-marketing issues.  
Please provide a call in number for this call. Clinical and non-clinical team member may be necessary.

Allison Meyer  
Sr. Regulatory Health Project Manager  
Division of Anesthesia, Analgesia and  
Addiction Products  
Office of New Drugs II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Bldg. 22, Rm. 3176  
Silver Spring, MD 20993  
301-796-1258  
301-796-9713 (fax)

**Meyer, Allison**

---

**From:** Meyer, Allison  
**Sent:** Friday, October 05, 2012 2:04 PM  
**To:** 'Aditi.Dron@fresenius-kabi.com'  
**Subject:** teleconference for Neostigmine

Aditi,  
We need to have a teleconference on October 18th at 3:30 pm (eastern time) to discuss some post-marketing issues.  
Please provide a call in number for this call. Clinical and non-clinical team member may be necessary.

Allison Meyer  
Sr. Regulatory Health Project Manager  
Division of Anesthesia, Analgesia and  
Addiction Products  
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10903 New Hampshire Avenue  
Bldg. 22, Rm. 3176  
Silver Spring, MD 20993  
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301-796-9713 (fax)

**Meyer, Allison**

---

**From:** Meyer, Allison  
**Sent:** Wednesday, August 29, 2012 4:13 PM  
**To:** 'Aditi.Dron@fresenius-kabi.com'  
**Subject:** RE: Neostigmine NDA 203629 - Marketing Data

Please confirm that the neostigmine that you have been marketing for the last 20 years, contains the same level of phenol in the proposed drug product formulation. If not, provide the years that the products containing phenol have been marketed. Confirm the difference between the two neostigmine codes in the table below.

Allison

---

**From:** Aditi.Dron@fresenius-kabi.com [mailto:Aditi.Dron@fresenius-kabi.com]  
**Sent:** Wednesday, August 29, 2012 3:24 PM  
**To:** Meyer, Allison  
**Subject:** Neostigmine NDA 203629 - Marketing Data

Dear Ms. Meyer,

This is in reference to your request shown below for marketing data for Neostigmine Methylsulfate Injection by Fresenius Kabi USA, LLC (formerly APP Pharmaceuticals, LLC).

**Agency Request** (received 8/22/12): "How long have you been marketing the formulation that you are seeking to have approved and approximately how many vials of that formulation have been sold?"

**Fresenius Kabi USA Response:** We have been marketing these formulations for over 20 years. The distribution data for the past 10 years is provided in the table below:

Year	Neostigmine code 38210 (# of units)	Neostigmine code 38310 (# of units)	Neostigmine Total (# of units)
2002	(b) (4)	(b) (4)	(b) (4)
2003	(b) (4)	(b) (4)	(b) (4)
2004	(b) (4)	(b) (4)	(b) (4)
2005	(b) (4)	(b) (4)	(b) (4)
2006	(b) (4)	(b) (4)	(b) (4)
2007	(b) (4)	(b) (4)	(b) (4)
2008	(b) (4)	(b) (4)	(b) (4)
2009	(b) (4)	(b) (4)	(b) (4)
2010	(b) (4)	(b) (4)	(b) (4)
2011	(b) (4)	(b) (4)	(b) (4)
2012 (year to date)	(b) (4) (year to date)	(b) (4) (year to date)	(b) (4) (year to date)

Please feel free to contact me in case there are any further questions or comments regarding this NDA.

Sincerely,

Aditi Dron  
Regulatory Affairs Manager  
Fresenius Kabi USA, LLC

Phone: 847-330-3898  
Fax: 847-413-8570  
Email: aditi.dron@fresenius-kabi.com

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## **Meyer, Allison**

---

**From:** Meyer, Allison  
**Sent:** Wednesday, August 29, 2012 4:07 PM  
**To:** 'Aditi.Dron@fresenius-kabi.com'  
**Subject:** RE: Neostigmine NDA 203629 - new Contact Info

Aditi,  
Thank you for that information. I will need you to send me a word version of the label with line numbers included. Also, I will need an annotated version with the specific details of where these references can be located.

Thank you,  
Allison

---

**From:** Aditi.Dron@fresenius-kabi.com [mailto:Aditi.Dron@fresenius-kabi.com]  
**Sent:** Tuesday, August 28, 2012 5:09 PM  
**To:** Meyer, Allison  
**Subject:** RE: Neostigmine NDA 203629 - new Contact Info

Dear Ms. Meyer,

We have been able to expedite the submission of this amendment. It will be submitted tomorrow. It will contain the (b) (4) and the Ames study.

Sincerely,

Aditi Dron  
Regulatory Affairs Manager  
Fresenius Kabi USA, LLC

Phone: 847-330-3898  
Fax: 847-413-8570  
Email: aditi.dron@fresenius-kabi.com

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attachments) is strictly prohibited and may be subject to legal sanction. If you have received this transmission in error, please permanently delete it, and notify us immediately. Thank you.

From: "Meyer, Allison" <Allison.Meyer@fda.hhs.gov>  
To: "Aditi.Dron@fresenius-kabi.com" <Aditi.Dron@fresenius-kabi.com>  
Date: 08/27/2012 02:48 PM  
Subject: RE: Neostigmine NDA 203629 - new Contact Info

---

Is it possible that we might receive these amendments by Wednesday?

Thanks,  
Allison

---

**From:** Aditi.Dron@fresenius-kabi.com [<mailto:Aditi.Dron@fresenius-kabi.com>]  
**Sent:** Monday, August 27, 2012 1:36 PM  
**To:** Meyer, Allison  
**Subject:** Neostigmine NDA 203629 - new Contact Info

Dear Ms. Meyer,

I am the new regulatory contact for Fresenius Kabi USA's Neostigmine Methylsulfate Injection NDA 203629. My contact information is provided below.

As informed during our telephone conversation earlier this afternoon, the Amendment to provide (b) (4) [REDACTED] the Ames Study is expected to be submitted this Friday August 31, 2012.

Please feel free to contact me in case of any comments or questions regarding this NDA.

Sincerely,

Aditi Dron  
Regulatory Affairs Manager  
Fresenius Kabi USA, LLC

Phone: 847-330-3898  
Fax: 847-413-8570  
Email: [aditi.dron@fresenius-kabi.com](mailto:aditi.dron@fresenius-kabi.com)

THIS TRANSMISSION CONTAINS INFORMATION INTENDED FOR THE EXCLUSIVE USE OF THE INDIVIDUAL OR ENTITY TO WHOM IT IS ADDRESSED, AND MAY CONTAIN INFORMATION THAT IS PROPRIETARY, PRIVILEGED, CONFIDENTIAL, AND/OR OTHERWISE EXEMPT FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the intended recipient (or agent responsible for delivering this transmission to the intended recipient), you are hereby notified that any review, printing, copying, disclosure, distribution, transmission or use of this information (including any attachments) is strictly prohibited and may be subject to legal sanction. If you have received this transmission in error, please permanently delete it, and notify us immediately. Thank you.

## Meyer, Allison

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**From:** Meyer, Allison  
**Sent:** Thursday, October 18, 2012 3:57 PM  
**To:** Aditi.Dron@fresenius-kabi.com; grace.burbulys@fresenius-kabi.com  
**Subject:** PMR Milestones Fresenius Kabi Neostigmine NDA 203629

**Attachments:** PMR Milestones Fresenius Kabi Neostigmine NDA 203629.doc

Please return the document below with proposed timelines.

---



PMR Milestones  
Fresenius Kabi ...

Allison Meyer  
Sr. Regulatory Health Project Manager  
Division of Anesthesia, Analgesia and  
Addiction Products  
Office of New Drugs II  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Bldg. 22, Rm. 3176  
Silver Spring, MD 20993  
301-796-1258  
301-796-9713 (fax)

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/s/  
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ALLISON MEYER  
01/28/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

## REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

**\*\*Please send immediately following the Filing/Planning meeting\*\***

TO:  
**CDER-DDMAC-RPM**

FROM: (Name/Title, Office/Division/Phone number of requestor)

Allison Meyer, RPM, x61258  
ODEII/DAAAP

REQUEST DATE  
1/7/13

IND NO.

NDA/BLA NO.  
203629

TYPE OF DOCUMENTS  
(PLEASE CHECK OFF BELOW) Package Insert

NAME OF DRUG  
Neostigmine Methylsulfate

PRIORITY CONSIDERATION  
Standard

CLASSIFICATION OF DRUG  
NMB

DESIRED COMPLETION DATE  
(Generally 1 week before the wrap-up meeting)  
1/14/13

NAME OF FIRM:  
Fresenius-Kabi

PDUFA Date: 1/29/13

### TYPE OF LABEL TO REVIEW

**TYPE OF LABELING:**

(Check all that apply)

- PACKAGE INSERT (PI)  
 PATIENT PACKAGE INSERT (PPI)  
CARTON/CONTAINER LABELING  
MEDICATION GUIDE  
 INSTRUCTIONS FOR USE (IFU)

**TYPE OF APPLICATION/SUBMISSION**

- ORIGINAL NDA/BLA  
 IND  
 EFFICACY SUPPLEMENT  
 SAFETY SUPPLEMENT  
 LABELING SUPPLEMENT  
 PLR CONVERSION

**REASON FOR LABELING CONSULT**

- INITIAL PROPOSED LABELING  
 LABELING REVISION

**EDR link to submission: labeling sent via email**

**Please Note:** There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

**COMMENTS/SPECIAL INSTRUCTIONS:**

Mid-Cycle Meeting: [Insert Date]  
Labeling Meetings: [Insert Dates]  
Wrap-Up Meeting: [Insert Date]

SIGNATURE OF REQUESTER

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)  
x eMAIL

HAND

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/s/  
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ALLISON MEYER  
01/08/2013



NDA 203629

**REVIEW EXTENSION –  
MAJOR AMENDMENT**

Fresenius Kabi USA, LLC  
1501 E. Woodfield Road  
Suite 300 East  
Schaumburg, IL 60173

Attention: Aditi Dron  
Manager, Regulatory Affairs

Dear Ms. Dron:

Please refer to your December 29, 2011, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Neostigmine Methylsulfate Injection, USP.

On September 14, 2012, we received your September 14, 2012, solicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is January 29, 2013.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by January 8, 2013.

If you have any questions, call me, at (301) 796-1258.

Sincerely,

*{See appended electronic signature page}*

Allison Meyer  
Sr. Regulatory Health Project Manager  
Division of Anesthesia, Analgesia, and  
Addiction Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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ALLISON MEYER  
10/03/2012



NDA 203629

**INFORMATION REQUEST**

APP Pharmaceuticals, LLC  
Attention: James Harn  
Manager of Regulatory Affairs  
1501 East Woodfield Road, Suite 300E  
Schaumburg, Illinois 60173

Dear Mr. Harn:

Please refer to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Neostigmine Methylsulfate Injection.

We are reviewing the Chemistry, Manufacturing and Control section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your supplemental application.

1. Submit a categorical exclusion request under 21 CFR 25.31(b) or an Environmental Assessment if introductions are above 1 ppb, pursuant to the recommendations outlined in the following documents:
  - <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm088969.htm> and
  - <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm088977.htm>
2. State whether extraordinary circumstances exist as per 21CFR 25.21

If you have questions, call LCDR Luz E Rivera, Regulatory Project Manager, at (301) 796-4013.

Sincerely,

*{See appended electronic signature page}*

Prasad Peri, Ph.D.  
Branch Chief, Branch VIII  
Division of New Drug Quality Assessment III  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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PRASAD PERI  
07/12/2012



NDA 203629

**INFORMATION REQUEST**

APP Pharmaceuticals, LLC  
Attention: James Harn  
Manager of Regulatory Affairs  
1501 East Woodfield Road, Suite 300 East  
Schaumburg, IL 60173

Dear Mr. Harn:

Please refer to your New Drug Application (NDA) dated December 28, 2011 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Neostigmine Methylsulfate Injection, USP, 0.5 mg/mL and 1.0 mg/mL.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Information Request letters have been sent to the holders of DMF (b) (4) and (b) (4). Discuss with the holders to resolve the issues pertinent to the drug substance and container/closure system.
2. Provide validation data for all the proposed hold times for future commercial drug product manufacturing.
3. Provide qualitative and quantitative extractable profile of the rubber stoppers and demonstrate with data that they do not leach into the drug product during shelf life.
4. Provide updated stability data from all 4 registration batches, including sterility testing results.
5. State whether there have been any changes in the formulation, sterilization process, and container/closure system between the registration batches and historical batches, for which supporting stability data are referenced.

If you have any questions, call LT Luz E Rivera, Regulatory Project Manager, at (301) 796 4013.

Sincerely,

*{See appended electronic signature page}*

Prasad Peri, PhD  
Branch Chief, Branch VIII  
Division of New Drug Quality Assessment III  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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PRASAD PERI  
06/22/2012



NDA 203629

**FILING COMMUNICATION**

APP Pharmaceuticals, LLC  
1501 East Woodfield Road  
Suite 300 East  
Schaumburg, IL 60173

Attention: James Harn  
Manager of Regulatory Affairs

Dear Mr. Harn:

Please refer to your New Drug Application (NDA) dated December 28, 2011, received December 29, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Neostigmine Methylsulfate Injection, USP.

We also refer to your amendments dated January 13 and 20, 2012.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is October 29, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by October 6, 2012.

During our filing review of your application, we identified the following potential review issue:

As per the 1999 FDA Guidance for Industry titled "Container Closure Systems for Packaging Human Drugs and Biologics," injectable drug product container closures present the highest degree of concern regarding the likelihood of potentially leaching harmful substances into the drug product solution. Although you have submitted results of USP testing for the (b) (4)

(b) (4) gray (b) (4) rubber stopper, your submission does not appear to include an extraction study to determine which chemical species may migrate into the dosage form (and at what concentration) or a toxicological evaluation of those specific substances which are extracted to justify the safe level of exposure via this drug product. As noted in the guidance, data from USP Biological Reactivity Tests and USP Elastomeric Closures for Injections tests are typically considered sufficient evidence of material safety; however, given the presence of phenol in your drug product solution, we are not convinced that potentially novel compounds (chemical identity or concentration) will not leach from this stopper. Submit data from controlled extraction studies to qualitatively and quantitatively determine the chemical species which may migrate into the dosage form, and leachable data from long-term stability studies (taking into consideration the proposed shelf-life) to determine if the identified/specified extractables also leach into the drug product over time, and a toxicological risk assessment justifying the safety of the extractables and leachables taking into consideration the maximum daily dose of the identified materials for this drug product.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

Provide a method validation package.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

### **PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We note that you have not addressed how you plan to fulfill this requirement. Within 30 days of the date of this letter, please submit (1) a full waiver request, (2) a partial waiver request and a pediatric development plan for the pediatric age groups not covered by the partial waiver request, or (3) a pediatric drug development plan covering the full pediatric age range. All waiver requests must include supporting information and documentation. A pediatric drug development plan must address the indication proposed in this application.

If you request a full waiver, we will notify you if the full waiver is denied and a pediatric drug development plan is required.

If you have any questions, call Allison Meyer, Regulatory Project Manager, at (301) 796-1258.

Sincerely,

*{See appended electronic signature page}*

Bob A. Rappaport, M.D.  
Director  
Division of Anesthesia, Analgesia, and  
Addiction Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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RIGOBERTO A ROCA on behalf of BOB A RAPPAPORT  
03/12/2012



NDA 203629

**NDA ACKNOWLEDGMENT**

APP Pharmaceuticals, LLC  
1501 East Woodfield Road  
Suite 300 East  
Schaumburg, IL 60173

Attention: James Harn  
Manager of Regulatory Affairs

Dear Mr. Harn:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Neostigmine Methylsulfate Injection, USP, 0.5 mg/mL and 1.0 mg/mL

Date of Application: December 28, 2011

Date of Receipt: December 29, 2011

Our Reference Number: NDA 203629

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 27, 2012, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anesthesia, Analgesia, and Addiction Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, call me, at (301) 796-1258.

Sincerely,

*{See appended electronic signature page}*

Allison Meyer  
Sr. Regulatory Health Project Manager  
Division of Anesthesia, Analgesia,  
and Addiction Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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ALLISON MEYER  
01/05/2012



PIND 106574

**MEETING MINUTES**

APP Pharmaceuticals  
1501 East Woodfield Road  
Suite 300 East  
Schaumburg, IL 60173

Attention: Dale Carlson  
Director, Regulatory Affairs

Dear Mr. Carlson:

Please refer to your Pre-Investigational New Drug file for Neostigmine Methylsulfate Injection.

We also refer to the meeting between representatives of your firm and the FDA on December 22, 2009. The purpose of the meeting was to discuss your plans to submit a 505(b)(2) New Drug Application (NDA).

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact me at [allison.meyer@fda.hhs.gov](mailto:allison.meyer@fda.hhs.gov) or 301-796-1258.

Sincerely,

*{See appended electronic signature page}*

Allison Meyer  
Regulatory Project Manager  
Division of Anesthesia, Analgesia,  
and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure—Meeting Minutes

**MEMORANDUM OF MEETING MINUTES**

**MEETING DATE/TIME:** December 22, 2009; 10:30 AM

**APPLICATION:** NDA 021038  
**PRODUCT:** Neostigmine Methylsulfate Injection, USP  
**INDICATION:** reversal neuromuscular blocking agent  
**SPONSOR:** APP Pharmaceuticals  
**TYPE OF MEETING:** Type B  
**MEETING CHAIR:** Rigoberto Roca, MD, Deputy Division Director  
 Division of Anesthesia, Analgesia and Rheumatology  
 Products (DAARP)  
**MEETING RECORDER:** Allison Meyer, Regulatory Project Manager

<b>FDA Attendees</b>	<b>Title</b>
Bob Rappaport, MD	Director, DAARP
Rigoberto Roca, MD	Deputy Director, DAARP
Bindi Nikhar, MD	Clinical Team Leader, DAARP
Arthur Simone, MD, PhD	Medical Officer, DAARP
Sayed Al Habet, PhD	Clinical Pharmacology Reviewer
Suresh Doddapaneni, PhD	Deputy Director, Division of Clinical Pharmacology II
Zengjun Xu, PhD	Pharmacology/Toxicology Reviewer
Adam Wasserman, PhD	Supervisor, Pharmacology/Toxicology
Sally Loewke	Unapproved Drugs Coordinator
Astrid Lopez-Goldberg	Regulatory Counsel, Office of Compliance
Danae Christodoulou, PhD	Pharmaceutical Assessment Lead, ONDQA
Allison Meyer	Regulatory Project Manager, DAARP
<b>Sponsor Attendees</b>	<b>Title</b>
Christopher P. Bryant PhD	Executive Vice President and Chief Scientific Officer
Lisa McChesney Harris, PhD	Vice President, Regulatory Affairs
David Bowman	Vice President, Product Development
Dale Carlson	Director, Regulatory Affairs
Russell Hunter, RAC	Director, Regulatory Affairs
Christine Voigt, PhD	Manager, Regulatory Affairs
Marie Ostman	Senior Technical Regulatory Consultant
Mike Worthen, MD	Anesthesiologist

## **BACKGROUND:**

Presented below are the Agency's December 22, 2009, comments and responses to questions in the background meeting package, followed by a summary of relevant discussion that took place at the meeting itself. The sponsor's questions are listed in *italics*, with Agency responses and comments in **bold**. Discussion that took place at the meeting is captured in normal text following the question to which it pertains.

### **Agency Comments and Responses to Questions:**

#### *Question 1*

*Does the Agency concur that the clinical efficacy and safety data documented in the medical literature is sufficient to support submission of a 505(b)(2) NDA for neostigmine methylsulfate injection used as a reversal agent to the neuromuscular blocking effects of nondepolarizing muscle relaxants in the adult population, without conducting additional clinical studies?*

#### **FDA Response**

**There is a substantial amount of literature assessing the clinical use of neostigmine for the proposed indication. The Agency's formal review of the literature and determination of its adequacy to support an approval action would be made following the submission of an NDA. The following points will be considered when the Agency makes its evaluation and should help guide you in both, determining whether there is need to supplement published data, and how to present the published data in an NDA submission.**

- **Data from well-designed, blinded, randomized, controlled clinical trials carry the most weight in determinations of safety and efficacy.**
- **Only data that are in the public domain or for which you have right of access can be considered for review purposes. Note, however, that having right of reference would permit submission of the NDA under 505(b)(1).**
- **Agency access to original protocols and raw data should be provided where possible. Lack of such access precludes assessment of data integrity and limits the evaluation of the adequacy of the trial design and conduct of the study.**
- **Each published study should be critically reviewed and its data organized to allow an organized assessment of efficacy and safety.**
- **Safety data should be integrated, to the extent possible, to create a safety database that can be analyzed according to subject demographics, dose of neostigmine evaluated, use of an anticholinergic, and neuromuscular blocking agent reversed.**
- **Efficacy data should be integrated according to the same parameters as the safety data.**

Discussion: The Sponsor stated that they have not conducted any clinical studies assessing neostigmine methylsulfate injection as a reversal agent to the neuromuscular blocking effects of nondepolarizing muscle relaxants in adult or pediatric patients. The Sponsor also stated that they do not have access to any clinical protocols or raw data from the published studies. The Sponsor believes that there is sufficient data within the published literature in the form of well-designed, blinded, randomized, controlled clinical trials to establish a satisfactory clinical safety and efficacy database; therefore, they have no plans to submit clinical raw data in the NDA. The Division stated that this would be a review issue, and the Division will consider the quality as well as the volume of data submitted. The Division requested that the Sponsor make a good faith effort to acquire protocols and the original clinical data.

The Division inquired if the Sponsor intended to seek the other indications currently in the label for neostigmine. The Sponsor responded that they only intended to pursue the “reversal of neuromuscular blocking agents” indication. The Division encouraged the Sponsor to pursue the other indications on the current product label as well and noted that these could be sought in a sequential fashion. The Division requested that the Sponsor document the use of neostigmine in other indications in their initial NDA submission.

The Sponsor asked whether the agency would accept, as part of the safety database, exposures to drug for an indications other than for reversal of the neuromuscular blocking effects of nondepolarizing muscle relaxants (e.g., myasthenia crisis, central anticholinergic syndrome), or for a route of administration other than intravenous. The Division stated that there might be difficulty combining safety data from additional indications, as the underlying medical condition of the patient, and route of administration for indications other than reversal of neuromuscular blockade may affect the data. The Division requested that the safety database focus on patients receiving neostigmine for the indication of reversal of the neuromuscular blocking effects of nondepolarizing muscle relaxants. Safety of neostigmine when used for other indications should be included in the NDA, but should be easily identified as such, and safety analyses should be conducted with and without the supporting safety data.

#### *Question 2*

*Does the Agency concur that the clinical efficacy and safety data documented in the medical literature is sufficient to support submission of a 505(b)(2) NDA for neostigmine methylsulfate injection used as a reversal agent to the neuromuscular blocking effects of nondepolarizing muscle relaxants in the pediatric population, without conducting additional clinical studies?*

#### **FDA Response**

**Refer to the response to Clinical Question #1. A similar approach should be taken for the pediatric patient population. PK, safety and efficacy data should be provided taking the following pediatric age groups into consideration:**

- **Neonate (< 1 month)**
- **Infant (1-24 months)**

- Child (pre-school) (2-6 years)
- Child (school-age) (6-12 years)
- Adolescent (12-16 years)

**Needed information that is not found or not adequately addressed in the literature will need to be supplemented by clinical trials in this patient population .**

Discussion: There was no further discussion on this question.

### *Question 3*

*Does the Agency concur that, in addition to the data accumulated over years of clinical use of IV neostigmine methylsulfate, the nonclinical information available in the literature and summarized in this information package sufficiently establishes the safety of Neostigmine Methylsulfate Injection, USP as a reversal agent to the neuromuscular blocking effects of nondepolarizing muscle relaxants and that additional nonclinical studies are not required to support a 505(b)(2) NDA submission?*

### **FDA Response**

**If you intend to submit a 505(b)(2) application that relies for approval on literature or other studies for which you have no right of reference but that are necessary for approval, you must establish that reliance on the studies described in the literature is scientifically appropriate. The non-clinical data included in this submission does not by itself appear sufficient to support the safety of human use of your product from a pharmacology and toxicology perspective. However, non-clinical studies may not be necessary for an NDA submission to support neostigmine due to the long history of human use. Nonclinical studies may be necessary to support novel excipients, leachables, and impurities or degradants in your drug product which are in excess of established guidelines. In particular:**

**Any novel excipients may need to be qualified for safety at the time of NDA submission, see *Guidance for Industry: Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients* which is available on the CDER web page at the following <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. As noted in the document cited above, “the phrase *new excipients* means any ingredients that are intentionally added to therapeutic and diagnostic products but which: (1) we believe are not intended to exert therapeutic effects at the intended dosage (although they may act to improve product delivery, e.g., enhancing absorption or controlling release of the drug substance); and (2) are not fully qualified by existing safety data with respect to the currently proposed level of exposure, duration of exposure, or route of administration.” Note that both the concentration of the excipient as well as the total amount administered must be within levels previously allowed in approved products.**

**Any impurity or degradation product that exceeds ICH thresholds may need to be adequately qualified for safety as per (ICHQ3A(R), ICHQ3B(R)) at the time of NDA submission.**

- **Adequate qualification would include:**
  - **Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies; e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.**
  - **Repeat dose toxicology of appropriate duration to support the proposed indication.**
- **Additionally, impurities or degradation products that contain structural alerts for mutagenicity may be held to more stringent standards of control. We recommend consideration of the draft *Guidance for Industry: Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches* available on the FDA website listed above.**
- **In module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), you must include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product, and how these levels compare to ICHQ3A and Q3B qualification thresholds along with a determination if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification thresholds should be adequately justified for safety from a toxicological perspective.**

**For potential leachables and extractables from the drug container closure system, you will need to provide a toxicological evaluation to determine the safe level of exposure via the labeled specified route of administration. The approach for toxicological evaluation of the safety of extractables must be based on good scientific principles and take into account the specific container closure system, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). This should be specifically discussed in module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. For additional guidance on extractables and leachables testing, consult the FDA Guidance document “Container Closure Systems for Packaging Human Drugs and Biologics”, USP <661>, and the PQRI leachables/extractables recommendations to the FDA found at [http://www.pqri.org/pdfs/LE\\_Recommendations\\_to\\_FDA\\_09-29-06.pdf](http://www.pqri.org/pdfs/LE_Recommendations_to_FDA_09-29-06.pdf).**

**Although the Agency wishes to bring neostigmine under an approved NDA, should your drug product contain impurities, degradants, and/or leachables which exceed generally allowable levels and are not qualified for safety it may be necessary to demonstrate that the**

**approval of your product will not expose the public to a less safe version of neostigmine than other products which are currently found on the market.**

**We note that neostigmine does not appear to have information related to genetic or reproductive toxicology to inform the product label. While normally required for approval, these studies will not be required pre-approval but would be Post-Marketing Requirements unless sufficient additional data is provided to address these concerns and allow for adequate labeling.**

Discussion: The Sponsor asked for clarification to better understand how non-clinical studies “may not be necessary” due to the long history of neostigmine human use. The Division stated that if there is sufficient clinical data, nonclinical data would not be necessary to support the application as it relates to the active pharmaceutical ingredient.

The Sponsor stated that it is their position that none of the excipients in the drug product are considered novel (i.e., phenol, sodium acetate). Furthermore, the level of phenol in the neostigmine formulation is below levels used in other FDA-approved products; therefore, nonclinical studies for excipients are not required. The Sponsor will test new batches for impurities, and if the impurities present at less than ICHQ3B threshold levels, the Sponsor would like to eliminate additional testing to qualify these in nonclinical studies. It was the position of the Sponsor that if impurities for the DP are greater than ICHQ3B threshold levels, these impurities may be qualified against currently marketed products for comparable impurity profile and intensities of the individual peaks.

The Division stated that the impurities will need to be characterized and reported and that impurities greater than the ICHQ3B threshold can potentially be justified for the NDA through comparison against currently marketed products. In addition, the Sponsor needs to provide evidence that the excipients in the product are already contained in currently approved products with levels and duration which cover the proposed use.

#### *Question 4*

*Does the Agency concur that for the purpose of filing a new drug application (NDA), two exhibit batches for each of the two strengths of Neostigmine Methylsulfate Injection, USP are sufficient to support a 505(b)(2) marketing application?*

#### **FDA Response**

**Your proposal to submit two primary stability batches for each of the two strengths is acceptable.**

**Monitor and report impurities/degradants as per ICHQ3B. However, for impurities that contain a structural alert for mutagenicity you will need to develop appropriate assay(s) and provide validation as per ICHQ2 to detect these impurities/degradants at very low levels.**

**Regarding safety evaluation/qualification of impurities/degradants, refer to the non-clinical comments, for Question 3.**

Discussion: There was no further discussion on this question.

*Question 5*

*Does the Agency concur that for the purpose of filing a new drug application (NDA), real-time data, obtained from testing only at  $25\pm 2^{\circ}\text{C}$ ,  $60\pm 5\%$  RH through 6 months, and accelerated data, obtained from testing at  $40\pm 2^{\circ}\text{C}$ ,  $75\pm 5\%$  RH through 6 months would be sufficient to support a proposed shelf-life for the product of 24 months?*

**FDA Response**

**No, we do not concur. While the proposed real time and accelerated data stated above may be acceptable for filing, it may not necessarily support a shelf life of 24 months. We remind you that expiration dating will be assessed as per ICHQ1E during the NDA review and will be based on available real time primary and supporting stability data and statistical analysis evaluation, if applicable.**

**We strongly recommend that you submit the maximum available stability data for your primary stability batches at the time of NDA submission. While every effort will be made to review any stability amendments to the NDA, their review will depend on the timeliness of submission, extent of submitted data, and available resources. Therefore, per GRMP guidelines, we may not be able to review amendments submitted to the NDA during the review cycle.**

**In addition, provide:**

**Photostability data, as per ICHQ1B;**

**Data on physicochemical compatibility with atropine, other co-administered drugs and diluents;**

**Include data on particulates, neostigmine assay and levels of impurities/degradants.**

Discussion: The Sponsor stated that they will provide as much real time and accelerated stability data for registration lots as is available at the time of submission, with no less than 6 months of data included in the NDA submission. In addition, 24-month real time supportive data will be provided for lots manufactured with the same formulation and using the same commercial equipment, in the NDA submission. The Sponsor asked if the stability data for the registration and stability lots were statistically poolable, and supported a 24-month shelf-life, could a 24-month shelf life be requested in the NDA submission. The Division asked if the formulation of the proposed drug product is the same as the currently marketed product, and the Sponsor stated that it is. If the formulation and container closure system of the drug product in the marketing application are identical to the currently marketed product then the data can be used to support a longer shelf life. The Division stated that impurities and degradants should be monitored in the drug product and that no information (on impurities or degradants) was provided in the briefing package. This information should be provided in the NDA. The Division reiterated that

expiration dating will be assessed during NDA review and referred the sponsor to ICH Q1E (Evaluation of Stability Data) for the requirements on expiration dating.

The Sponsor stated that they will generate compatibility data with co-administered diluents and drugs, which include strength, degradants and particulate matter for the IV diluents recommended for use with neostigmine in the appropriate concentration range.

When neostigmine is administered as a reversal agent to the neuromuscular blocking effects of nondepolarizing muscle relaxants, atropine or glycopyrrolate are administered as a concomitant medication in order to prevent possible side effects of neostigmine. In the current label, it states that atropine sulfate be given IV using a separate syringe; therefore, the Sponsor did not consider neostigmine to be "co-administered" with atropine or glycopyrrolate. The Division acknowledged what the label stated, but noted that neostigmine and atropine or glycopyrrolate are frequently mixed in the same syringe in clinical practice and, therefore, an *in vitro* physicochemical compatibility study should be conducted.

**Additional CMC Developmental Comments:**

**Provide a specification for osmolality for the drug product.**

**Provide a list of all manufacturing and testing facilities, in alphabetical order, statement about their cGMP status and whether they are ready for inspections at the time of NDA submission. For all manufacturing sites, provide a contact name, telephone number, facsimile number and email address. Clearly specify the responsibilities of each facility, and which sites are intended to be primary or alternate sites. Note that facilities with unacceptable cGMP compliance may risk approvability of the NDA.**

**Additional Clinical Pharmacology Comments:**

**From the information provided in the submission, it does not appear that you have completely captured all available Clinical Pharmacology information. As such, the Agency cannot comment on the adequacy of the Clinical Pharmacology information to support the submission of a 505 (b)(2) NDA. You are advised to summarize all available Clinical Pharmacology information related to pharmacokinetics, distribution, metabolism, elimination, dose-response, and special populations (such as drug-drug interactions, hepatic impairment, renal impairment, elderly, gender, pediatrics, etc). Where information is not available or is not pertinent to this drug, this should be stated explicitly. Based on the drug's properties, if a particular aspect is not applicable, an explanation as to why it is not applicable should be provided. Overall, you are expected to address comprehensively all aspects of Clinical Pharmacology information. Follow the current Physician Labeling Rule format for the content of the clinical pharmacology section of the label.**

**It appears that by not proposing to conduct any PK studies, you are expecting to seek a biowaiver. If this is the intent, then submit the biowaiver request with supporting information.**

Discussion: The Sponsor stated that they intend to limit the indication for neostigmine as a "reversal agent for the neuromuscular blocking effects of nondepolarizing muscle relaxants," and the route of administration to intravenous administration only. They asked for clarification of a biowaiver in this circumstance.

The Division stated that this is a regulatory requirement for 505 (b)(2) submissions and one way for them to address this requirement is to assess whether the current formulation of the drug product was used in the PK/clinical studies cited in the literature and identify those studies. If the literature articles did not use the Sponsor's formulation, then the Sponsor should try to relate the formulations used in the clinical literature to the Sponsor's formulation.

**Action Items:**

1. The Sponsor will rely on literature review for the safety and efficacy data, and make a good faith effort to obtain original data and protocols where possible.
2. The integrated safety database will be specific to studies conducted for the indication sought; safety in other indications will be presented separately as supportive data.
3. Justification of the pharmacopeial status and safety of the excipients will be submitted.
4. Impurity levels will be reported and qualified according to ICH Q3B, or if levels are in excess of established threshold limits they may be justified for the NDA through comparison to impurity levels of neostigmine products currently on the market.
5. Expiry dating will be supported with stability data from registration batches and currently marketed product.
6. Physical compatibility of atropine and glycopyrrolate with neostigmine will be evaluated.
7. Justification and request for a biowaiver will be provided in the NDA.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-106574	GI-1	APP PHARMACEUTICA LS	Neostigmine Methylsulfate Injections, USP

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

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/s/

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ALLISON MEYER  
02/01/2010