

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203629Orig1s000

CHEMISTRY REVIEW(S)



Public Health Service

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

Memorandum

Date: December 22, 2014

To: DARRTS and Panorama

From: Julia Pinto, Ph.D.

Subject: CMC Memo to File Regarding NDA 203629
Neostigmine Methylsulfate Injection, USP

Applicant: Fresenius Kabi USA, LLC
3 Corporate Drive, Lake Zurich, IL 60047

Product: Neostigmine Methylsulfate Injection, USP

The original NDA, submitted December 29, 2011, and reviewed by Edwin Jao, Ph.D was recommended as approvable pending an overall satisfactory recommendation by the Office of Compliance. Upon inspection of the Grand Island, NY manufacturing facility, several deficiencies were cited by the FDA field Inspector. As of the filing of the resubmission, January 2014, the Grand Island facility is ready for inspection and the deficiencies have been resolved. Consequently, the Office of Compliance has given an overall satisfactory recommendation for this NDA on Dec 22th 2014 (attached below).

Conclusion: Therefore since all outstanding inspection issues have been adequately resolved, and there are no additional CMC changes, this NDA is recommended for approval, from the CMC perspective.

Julia C. Pinto, Ph.D.

Acting Branch Chief, Branch VIII
ONDQA

Overall Manufacturing Inspection Recommendation | [Next task »](#)

NDA 203629-Orig1-Resubmission/Class 2(21)

Task Details

Task Data

Open Issues

More ▾

Facility Inspection - Overall Application Recommendation

Facility Inspection - Overall Application Recommendation

Approve

Facility Inspection - Overall Application Re-evaluation Date

6/1/15

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/s/

JULIA C PINTO
12/22/2014

NDA 203, 629

NEOSTIGMINE METHYLSULFATE INJECTION, USP

Fresenius Kabi USA, LLC

Chemistry Review #1

January 22, 2013

Recommendation: Complete Response

Edwin Jao, Ph.D.

ONDQA/Division III/Branch VIII

for

Division of Anesthesia, Analgesia, and Addiction Products Product

Chemistry Review Data Sheet

1. NDA 203629
2. REVIEW #:2
3. REVIEW DATE: **January 22, 2013**
4. REVIEWER: Edwin Jao, Ph.D.
5. Related DOCUMENTS:

Previous DocumentsDocument Date

Original NDA
Amendment
Amendment
Amendment
Amendment

12-29-2011
06-05-2012
8-1-2012
9-14-2012
9-28-2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Amendment 9-14-2012

Amendment 9-28-2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Fresenius Kabi USA, LLC
Address:	1501 EastWoodfield Road, Suite 300 Schaumburg, IL 60173
Representative:	James Harn
Telephone:	847 517-5767

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:

b) Non-Proprietary Name (USAN): Neostigmine Methylsulfate Injection, USP

c) Code Name: none provided

d) Chem. Type/Submission Priority:

- Chem. Type: 5 (new manufacturer)
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY:

anticholinesterase agent

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY:

0.5 mg/ml, 1.0 mg/ml

13. ROUTE OF ADMINISTRATION: IV

14. Rx/OTC DISPENSED: Rx OTC

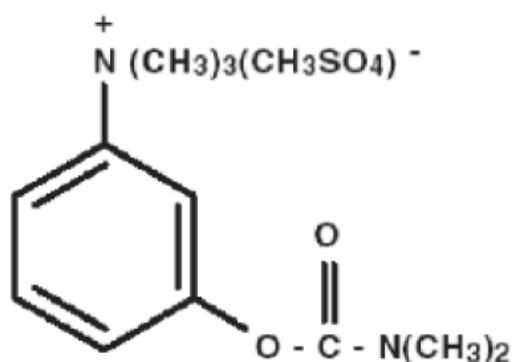
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

____ SPOTS product

 X Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Neostigmine Methylsulfate

Empirical Formula: C₁₃H₂₂N₂O₆S

Molecular Weight: 334.39

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYP E	HOLDER	ITEM REFERENCED	CODE	STATUS ²	DATE REVIEW COMPLE TED	COMM ENTS
(b) (4)	II	(b) (4)	(b) (4)	1	adequate	12/21/2012	(b) (4)
	III			4	adequate		

(b) (4)	(b) (4)				(b) (4)
III		4	adequate		
III		1,4	adequate	9/15/2012	

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
na		

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	na		
EES	withhold	1/18/2013	
Pharm/Tox	Approval	9/19/2012	Dr. Huiqing Hao
Clinpharm	Approval	9/19/2012	Dr. Lokesh Jain
LNC	N.A.		

Methods Validation	Not necessary		
EA	acceptable	9/20/2012	Raanan Bloom
Microbiology	acceptable	9/10/2012	Vinayak Pawar
CDRH	Not necessary		

Executive Summary Section

The Chemistry Review for NDA 22-472**The Executive Summary****I. Recommendations****A. Recommendation and Conclusion on Approvability**

From the ONDQA perspective, this NDA is recommended for complete response (CR) based on the final **withhold** recommendation from the Office Compliance.

Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

no

II. Summary of Chemistry Assessments**Basis for Approvability or Not-Approval Recommendation**

1. *The recommendation from the Office of Compliance for this NDA is “withhold” as 1/18/2013*

III. Administrative**A. Reviewer’s Signature**

(See appended electronic signature page)

Edwin Jao, Ph. D., CMC Reviewer, Branch VIII, ONDQA

B. Endorsement Block

Prasad Peri, Ph. D., Branch Chief, Branch VIII, ONDQA.

C. CC Block

Ramesh Raghavachari, Ph. D., CMC Lead, Division III, ONDQA

APPEARS THIS WAY ON THE ORIGINAL

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/s/

EDWIN JAO
01/22/2013

PRASAD PERI
01/29/2013
I concur

NDA 203, 629

NEOSTIGMINE METHYLSULFATE INJECTION, USP

Fresenius Kabi USA, LLC

Chemistry Review #1

December 21, 2012

Recommendation: Complete Response

Edwin Jao, Ph.D.

ONDQA/Division III/Branch VIII

for

Division of Anesthesia, Analgesia, and Addiction Products Product

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Chemistry Review Data Sheet

1. NDA 203629
2. REVIEW #:2
3. REVIEW DATE: **December 21, 2012**
4. REVIEWER: Edwin Jao, Ph.D.
5. Related DOCUMENTS:

Previous DocumentsDocument Date

Original NDA
Amendment
Amendment
Amendment
Amendment

12-29-2011
06-05-2012
8-1-2012
9-14-2012
9-28-2012

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Amendment 9-14-2012

Amendment 9-28-2012

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Address:	1501 EastWoodfield Road, Suite 300 Schaumburg, IL 60173
Representative:	James Harn
Telephone:	847 517-5767

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:

b) Non-Proprietary Name (USAN): Neostigmine Methylsulfate Injection, USP

c) Code Name: none provided

d) Chem. Type/Submission Priority:

- Chem. Type: 5 (new manufacturer)
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY:

anticholinesterase agent

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY:

0.5 mg/ml, 1.0 mg/ml

13. ROUTE OF ADMINISTRATION: IV

14. Rx/OTC DISPENSED: Rx OTC

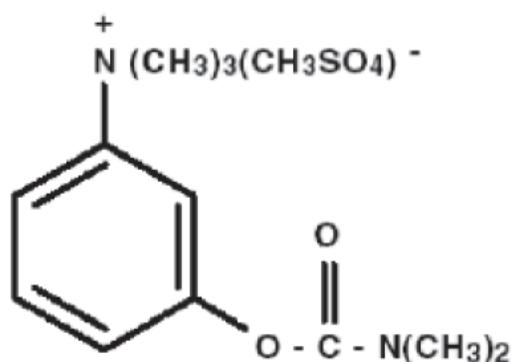
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product

 X Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Neostigmine Methylsulfate

Empirical Formula: C₁₃H₂₂N₂O₆S

Molecular Weight: 334.39

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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	III			4	adequate		

(b) (4)	(b) (4)				(b) (4)
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III		1,4	adequate	9/15/2012	

¹ Action codes for DMF Table:

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Other codes indicate why the DMF was not reviewed, as follows:

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6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
na		

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	na		
EES	withhold	9/19/2012	
Pharm/Tox	Approval	9/19/2012	Dr. Huiqing Hao
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LNC	N.A.		

Methods Validation	Not necessary		
EA	acceptable	9/20/2012	Raanan Bloom
Microbiology	acceptable	9/10/2012	Vinayak Pawar
CDRH	Not necessary		

Executive Summary Section

The Chemistry Review for NDA 22-472

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

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

Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

no

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The **drug substance** is neostigmine methylsulfate, USP. It is not a NME. The characterization of this compound has been well documented in the literature, and the manufacturer has adequately confirmed the structure of the drug substance they produced. While it contains structural alert moieties ((b) (4) and (b) (4)), it is not genotoxic based on non-clinical data (see pharmtox team review). Neostigmine Methylsulfate, USP is manufactured by (b) (4). The establishment received "Acceptable" recommendation from the Office of Compliance on 1/22/2012. This compound is prepared through multiple steps of synthesis. The detailed CMC information is incorporated by reference to DMF (b) (4) which is considered adequate to support this NDA. The proposed drug substance specification meets and exceeds that required by the USP monograph for neostigmine methylsulfate. The quality and stability of the registration batches of the drug substance Neostigmine Methylsulfate, USP are adequately demonstrated by release and stability data. The drug substance is packaged in (b) (4). There are no safety concerns for the container/closure system. The proposed retest period of (b) (4) months is supported by real time stability data.

The drug product is Neostigmine Methylsulfate Injection, USP, 0.5 mg/mL and 1.0 mg/mL, (b) (4) in 10 ml Type I USP glass vials, with rubber stopper and aluminum seal. Neostigmine Methylsulfate injection has been approved only for animal use (21CFR 522.1503), but not for human. Neostigmine Methylsulfate OPHTHALMIC SOLUTION was approved on 5/4/1939 (NDA 000654), but was withdrawn on 4/12/1996. Currently there are three companies marketing Neostigmine Methylsulfate injection (American Reagent, APP, and West-Ward Pharmaceuticals), and none of them have an approved NDA. Neostigmine Methylsulfate injection is on the drug shortage list. There is

Executive Summary Section

a current USP monograph for neostigmine methylsulfate injection. The excipients used in the formulation are liquefied phenol, sodium acetate, and water for injection. All the excipients are compendial. Liquefied Phenol (used as preservative) has been approved for IV drug product for up to 0.5% based on Inactive Ingredients database. There is no safety issue from CMC perspective. The drug product is manufactured by Fresenius Kabi USA, LLC (formerly APP). This establishment received a Withhold recommendation from the Office of Compliance on 2/24/2012, which remains effective. The environmental assessment for the drug product was submitted on 9/20, and considered acceptable by Dr. Raanan Bloom.

The manufacturing process of the drug product involves [REDACTED] (b) (4)

Adequate in-process and material controls are in place. The proposed drug product specification meets and exceeds that required by the USP monograph for neostigmine methylsulfate, injection. The [REDACTED] (b) (4) sterility controls have been evaluated by the microbiology team and are considered acceptable. Given that the drug product is an aqueous solution for injection, USP Type I glass generally satisfy safety and quality concerns. DMF [REDACTED] (b) (4) is referenced for the rubber stoppers, and is found adequate to support this NDA. Due to the presence of [REDACTED] (b) (4) % phenol in the formulation, there is potential for leachables from the rubber stoppers to be present in the drug product. Depending on the assessment of leachable data, additional controls might be necessary. However, since the same rubber stoppers are already used in two approved drug products with similar formulations and route of administration and given the marketing history of this drug product, the pharmtox team considers this issue can be further managed post approval. Release and stability data from two batches (pilot scale) each for the two strengths of the drug product are provided. Release batch data are acceptable per specification. Twelve months of stability data from the registration batches are provided. No significant trend is observed. Up to 45 months of supporting stability data (impurity profiles of the last testing points only) from historical batches (7 batches) are also provided. The requested shelf life of 24 months is supported by historical and registration stability data. All comments pertinent to labeling have been conveyed to applicant and satisfactorily resolved. .

B. Description of How the Drug Product is Intended to be Used

Neostigmine Methylsulfate Injection is administered IV for reversing non-depolarizing neuromuscular block

C. Basis for Approvability or Not-Approval Recommendation

- 1. The applicant of the NDA has provided sufficient information to assure the identity, strength, purity, and quality of the drug product.*

Executive Summary Section

2. *The recommendation from the Office of Compliance for this NDA is “withhold”.*

III. Administrative**A. Reviewer’s Signature**

(See appended electronic signature page)

Edwin Jao, Ph. D., CMC Reviewer, Branch VIII, ONDQA

B. Endorsement Block

Prasad Peri, Ph. D., Branch Chief, Branch VIII, ONDQA.

C. CC Block

Ramesh Raghavachari, Ph. D., CMC Lead, Division III, ONDQA

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/s/

EDWIN JAO
12/21/2012

PRASAD PERI
12/21/2012
I cocnur

NDA 203, 629

NEOSTIGMINE METHYLSULFATE INJECTION, USP

Fresenius Kabi USA, LLC

Chemistry Review #1

September 17, 2012

Recommendation: Complete Response

Edwin Jao, Ph.D.

ONDQA/Division III/Branch VIII

for

Division of Anesthesia, Analgesia, and Addiction Products Product

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 B. Description of How the Drug Product is Intended to be Used..... 10

 C. Basis for Approvability or Not-Approval Recommendation 10

III. Administrative.....10

 A. Reviewer’s Signature 10

 B. Endorsement Block 10

 C. CC Block..... 14

Chemistry Assessment 15

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....15

Chemistry Review Data Sheet

1. NDA 203629
2. REVIEW #:1
3. REVIEW DATE: August 29, 2012
4. REVIEWER: Edwin Jao, Ph.D.
5. Related DOCUMENTS:

Previous Documents

Original NDA
Amendment
Amendment

Document Date

12-29-2011
06-05-2012
8-1-2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original NDA dated 12-29-2011

Amendment dated 6-5-2012

Amendment dated 8-1-2012

Amendment dated 8-29-2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Fresenius Kabi USA, LLC
Address:	1501 EastWoodfield Road, Suite 300 Schaumburg, IL 60173
Representative:	James Harn
Telephone:	847 517-5767

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:

b) Non-Proprietary Name (USAN): Neostigmine Methylsulfate Injection, USP

c) Code Name: none provided

d) Chem. Type/Submission Priority:

- Chem. Type: 5 (new manufacturer)
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY:

anticholinesterase agent

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY:

0.5 mg/ml, 1.0 mg/ml

13. ROUTE OF ADMINISTRATION: IV

14. Rx/OTC DISPENSED: x_Rx OTC

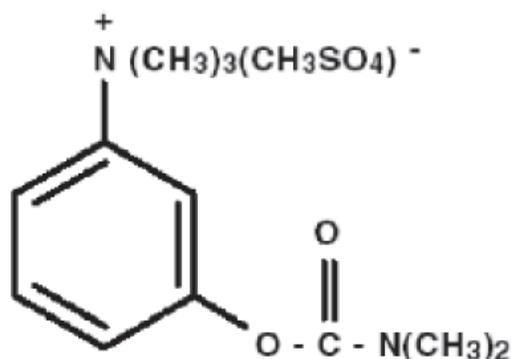
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

 SPOTS product

 X Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Neostigmine Methylsulfate



Empirical Formula: C₁₃H₂₂N₂O₆S

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A. DMFs:

DMF #	TYP E	HOLDER	ITEM REFERENCED	CODE	STATUS ²	DATE REVIEW COMPLE TED	COMM ENTS
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(b) (4)	(b) (4)				(b) (4)
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III		1,4	adequate	9/15/2012	

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6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
na		

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
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EES	withhold	9/19/2012	
Pharm/Tox	Approval	9/19/2012	Dr. Huiqing Hao

Clinpharm	Approval	9/19/2012	Dr. Lokesh Jain
LNC	N.A.		
Methods Validation	Not necessary		
EA	unacceptable	9/19/2012	
Microbiology	acceptable	9/10/2012	Vinayak Pawar
CDRH	Not necessary		

Executive Summary Section

The Chemistry Review for NDA 22-472

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the ONDQA perspective, this NDA is *not* recommended for approval per 21 CFR 314.125 (b)(1) in its present form until all the issues listed at the end of this review are satisfactorily resolved.

Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

pending

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The **drug substance** is neostigmine methylsulfate, USP. It is not a NME. The characterization of this compound has been well documented in the literature, and the manufacturer has adequately confirmed the structure of the drug substance they produced. While it contains structural alert moieties ((b)(4) and (b)(4)), it is not genotoxic based on non-clinical data (see pharmtox team review). Neostigmine Methylsulfate, USP is manufactured by (b)(4). The establishment received "Acceptable" recommendation from the Office of Compliance on 1/22/2012. This compound is prepared through multiple steps of synthesis. The detailed CMC information is incorporated by reference to DMF (b)(4). Multiple deficiencies pertinent to CMC of the drug substance, including designation of the starting material, in-process controls, and drug substance specification, were conveyed to the DMF holder and remain outstanding at the current time. While the DMF holder and applicant have promised to respond shortly, the DMF is considered inadequate to support this NDA at the current time (GRMP). The proposed drug substance specification meets and exceeds that required by the USP monograph for neostigmine methylsulfate. The quality and stability of the registration batches of the drug substance Neostigmine Methylsulfate, USP are adequately demonstrated by release and stability data. The drug substance is packaged in (b)(4). There are no safety concerns for the container/closure system. The proposed retest period of (b)(4) months is supported by real time stability data.

The drug product is Neostigmine Methylsulfate Injection, USP, 0.5 mg/mL and 1.0 mg/mL, (b)(4) in 10 ml Type I USP glass vials, with rubber stopper and aluminum seal. Neostigmine Methylsulfate injection has been approved only for animal

Executive Summary Section

use (21CFR 522.1503), but not for human. Neostigmine Methylsulfate OPHTHALMIC SOLUTION was approved on 5/4/1939 (NDA 000654), but was withdrawn on 4/12/1996. Currently there are three companies marketing Neostigmine Methylsulfate injection (American Reagent, APP, and West-Ward Pharmaceuticals), and none of them have an approved NDA. Neostigmine Methylsulfate injection is on the drug shortage list. There is a current USP monograph for neostigmine methylsulfate injection. The excipients used in the formulation are liquefied phenol, sodium acetate, and water for injection. All the excipients are compendial. Liquefied Phenol (used as preservative) has been approved for IV drug product for up to 0.5% based on Inactive Ingredients database. There is no safety issue from CMC perspective. The drug product is manufactured by Fresenius Kabi USA, LLC (formerly APP). This establishment received a Withhold recommendation from the Office of Compliance on 2/24/2012, which remains effective. Even though this drug product has been marketed in US, it has never been approved for its intended use. Dr. Raanan Bloom, the OPS Environmental Officer, recommended that the applicant submit a categorical exclusion request under 21 CFR 25.31(b) or an Environmental Assessment if introductions are above 1 ppb, regardless of the marketing history of this drug product. The environmental assessment for the drug product has not been completed.

The manufacturing process of the drug product involves

(b) (4)

Adequate in-process and material controls are in place. The proposed drug product specification meets and exceeds that required by the USP monograph for neostigmine methylsulfate, injection. The (b) (4) sterility controls have been evaluated by the microbiology team and are considered acceptable. Given that the drug product is an aqueous solution for injection, USP Type I glass generally satisfy safety and quality concerns. DMF (b) (4) is referenced for the rubber stoppers, and is found adequate to support this NDA. Due to the presence of (b) (4) % phenol in the formulation, there is potential for leachables from the rubber stoppers to be present in the drug product. Depending on the assessment of leachable data, , additional controls might be necessary. However, since the same rubber stoppers are already used in two approved drug products with similar formulations and route of administration and given the marketing history of this drug product, the pharmtox team considers this issue can be further managed post approval. Release and stability data from two batches (pilot scale) each for the two strengths of the drug product are provided. Release batch data are acceptable per specification. Twelve months of stability data from the registration batches are provided. No significant trend is observed. Up to 45 months of supporting stability data (impurity profiles of the last testing points only) from historical batches (7 batches) are also provided. The requested shelf life of 24 months is supported by historical and registration stability data. All comments pertinent to labeling have been conveyed to the team.

Executive Summary Section

B. Description of How the Drug Product is Intended to be Used

Neostigmine Methylsulfate Injection is administered IV for reversing non-depolarizing neuromuscular block

C. Basis for Approvability or Not-Approval Recommendation

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

III. Administrative**A. Reviewer’s Signature**

(See appended electronic signature page)

Edwin Jao, Ph. D., CMC Reviewer, Branch VIII, ONDQA

B. Endorsement Block

Prasad Peri, Ph. D., Branch Chief, Branch VIII, ONDQA.

C. CC Block

Ramesh Raghavachari, Ph. D., CMC Lead, Division III, ONDQA

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/s/

EDWIN JAO
09/20/2012

PRASAD PERI
09/20/2012
I concur

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Application: NDA 203629/000
Submission Date: 29-DEC-2011
Revised Date: 29-OCT-2012

Action Goal:
District Goal: 30-AUG-2012

Applicant: APP PHARMS LLC
1501 EAST WOODFIELD RD STE 300E
SCHAUMBURG, IL 60173

Brand Name: Neostigmine Methylsulfate Injections, US
Estab. Name:
Generic Name:

Priority: 3
Org. Code: 170

Product Number; Dosage Form; Ingredient; Strengths
001; INJECTABLE; NEOSTIGMINE METHYLSULFATE; .5MG
002; INJECTABLE; NEOSTIGMINE METHYLSULFATE; 1MG

Application Comment:

FDA Contacts:	S. PATWARDHAN	Project Manager	(HF-01)	3017964085
	E. JAO	Review Chemist		3017961684
	D. CHRISTODOULOU	Team Leader		3017961342

Overall Recommendation: WITHHOLD on 22-FEB-2012 by EES_PROD

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: 1321116 FEI: 3001833549
APP PHARMACEUTICALS, LLC.
3159 STALEY RD
GRAND ISLAND, NY 140722028

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER
DRUG SUBSTANCE RELEASE TESTER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE OTHER TESTER

Establishment Comment: APP SKOKIE, IL SITE IS RESPONSIBLE FOR PRODUCT DEVELOPMENT. ALTERNATE LAB FOR CHEMICAL TESTING FOR DRUG SUBSTANCE RELEASE.
ALTERNATE LAB FOR CHEMICAL TESTING FOR DRUG PRODUCT FOR RELEASE AND STABILITY TESTING (on 12-JAN-2012 by S. PATWARDHAN (HF-01) 3017964085)

Profile: (b) (4) SMALL VOLUME PARENTERAL DRUG **OAI Status:** OAI ALERT

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	17-JAN-2012				CHRISTODOULO
SUBMITTED TO DO	18-JAN-2012	10-Day Letter			SMITHDE
DO RECOMMENDATION WL WAS ISSUED ON 02/22/2012.	23-FEB-2012			WITHHOLD PEND REG ACTION - WARNING LTR	KGONZALE
OC RECOMMENDATION	24-FEB-2012			WITHHOLD DISTRICT RECOMMENDATION WARNING LETTER ISSUED	INYARDA

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: (b) (4) AADA:

- Responsibilities:
- DRUG SUBSTANCE MANUFACTURER
 - DRUG SUBSTANCE PACKAGER
 - DRUG SUBSTANCE RELEASE TESTER
 - DRUG SUBSTANCE STABILITY TESTER

Establishment Comment: (b) (4) RESPONSIBLE FOR DRUG SUBSTANCE MANUFACTURING, RELEASE/STABILITY TESTING, AND PACKAGING (on 12-JAN-2012 by S. PATWARDHAN (HF-01) 3017964085)
Profile: NON-STERILE API BY CHEMICAL SYNTHESIS OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	17-JAN-2012				CHRISTODOULO
SUBMITTED TO DO IS THIS AC THROUGH PDUFA?	18-JAN-2012	10-Day Letter			SMITHDE
DO RECOMMENDATION	21-JAN-2012			ACCEPTABLE BASED ON FILE REVIEW	PHILPYE
OC RECOMMENDATION	22-JAN-2012			ACCEPTABLE BASED ON PROFILE	SMITHDE

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Establishment Comment: DRUG PRODUCT ANTI-MICROBIAL EFFECTIVENESS TEST (AET) FOR PRODUCT DEVELOPMENT ONLY (ONE TIME TEST). THIS SITE WILL NOT BE USED FOR COMMERCIAL DRUG PRODUCT TESTING (on 24-FEB-2012 by S. PATWARDHAN (HF-01) 3017964085)
 Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	24-FEB-2012				PATWARDHAN
OC RECOMMENDATION	24-FEB-2012			ACCEPTABLE BASED ON PROFILE	INYARDA

Initial Quality Assessment
Office of New Drug Quality Assessment
Division III, Branch VIII
Division of Anesthesia, Analgesia and Addiction Products

OND Division: Anesthesia, Analgesia and Addiction, HFD-170
NDA: 203-629
Chemical Classification 2 S
Applicant: APP Pharmaceuticals
Stamp date: December 28, 2011
PDUFA Date: October 28, 2011
Division Goal Date: August 28, 2011
Trademark: NA
Established Name: Neostigmine Methylsulfate USP Injection,
USP Dosage Form: Injection, 0.5 mg/mL; 1 mg/mL
Route of Administration: Parenteral (IV)
Indication:
CMC Lead: Ramesh Raghavachari, Ph.D.

ONDQA Fileability: x
Comments for 74-Day Letter: x

Summary, Critical Issues and Comments:

Summary and Regulatory History:

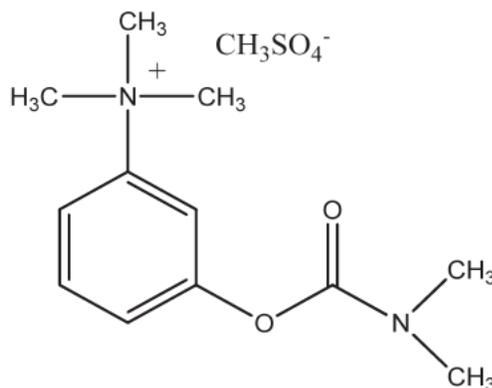
The application is submitted as a 505(b)(2), based on the approved NDA 00-654, Prostigmine (neostigmine bromide) ophthalmic solution, held by Roche and later discontinued. NDA 00-654 was approved in 1939. The Original submission was DESI designated. This file obtained from the document room labeled as 'Historical Document' contains correspondence from 1939 up to July 23, 1971. This file contains document which references the following NDAs with prostigmine in combination with other drug moieties. NDA 02-574 (Prostigmine & Morphine hypodermic tablets for solution and injection, NDA 02-575 (Prostigmine & Pantopan mixed alkaloids of Opium) hypodermic tablets for solution and injection, (b)(4) NDA 02-449 (Prostigmine & Atropine) ampoule for injection. All these products appear to have been withdrawn from the market. The structure of the drug substance presented in this historical file is the same as that of the API of this new NDA. This drug product appears to have been in the market since the nineteen seventies. Based on its regulatory history, the API in this NDA is not a New Molecular Entity.

This is a marketed unapproved product, by APP and is formulated with liquefied phenol, sodium acetate, (b)(4) acetic acid, sodium hydroxide, water for injection (b)(4) in 10 mL vials in two strengths (0.5 mg/mL and 1.0 mg/mL). The applicant has requested for a waiver of *in vivo* bioequivalence or bioavailability studies based on the literature reference. The proposed drug product will be available in the same configuration as the currently marketed unapproved drug product.

Review, Comments and Recommendations:

Drug Substance: Neostigmine Methylsulfate (USP)

Molecular Structure, Chemical Name, Molecular Formula and Molecular Weight



Chemical Name(s): (m-hydroxyphenyl) trimethylammonium methylsulfate dimethylcarbamate; Benzenamimium, 3[[[(dimethylamino) carbonyl]oxy]-N,N,N-trimethyl-,methylsulfate

Molecular formula: C₁₃H₂₂N₂O₆S

Molecular weight: 334.40

CAS Registry Number: [51-60-5]

The drug substance is manufactured by (b) (4) and is referenced to DMF # (b) (4) with a Letter of Authorization. The proposed facility has been submitted for cGMP compliance in EES. The DMF must be reviewed for adequacy of Drug Substance Data.

The drug substance impurities have been listed in the Quality Overall Summary as follows:

Table 2.3.S- 3 Impurities in the Drug Substance

Impurity Name	Structure	Origin
(b) (4)		

Impurity Name	Structure	Origin
(b) (4)		

Drug Substance Specifications:

The applicant has provided the following specifications for the drug substance and is a part of the DMF referenced.

Table 3.2.S.4.1- 1. Regulatory Specification for Neostigmine Methylsulfate, USP

Test	Acceptance Criteria	Test Method ¹
Appearance	White crystalline powder	Visual Examination
Identification:		
A. Infrared Absorption	A. A potassium bromide dispersion of the test specimen exhibits maxima only at the same wavelengths as a similar preparation of the corresponding USP Reference Standard.	A. USP <197K>
B. Diazobenzene-sulfonic acid	B. A cherry-red color is produced	B. USP
C. Sulfate	C. Responds to the tests for Sulfate	C. USP<191>
Melting Range	144 ° to 149 °C	USP <741> on dried basis
Loss on drying	NMT (b) (4)%	USP <731>
Residue on Ignition	NMT 0.1%	USP<281>
Chloride	No opalescence is produced immediately	USP
Sulfate ion	No turbidity is produced immediately	USP
Assay	98.0 to 102.0% (dried basis)	10-08-03-6654 HPLC
Impurities by HPLC		
(b) (4)	A. NMT (b) (4)%	A. 10-08-03-6654
(b) (4)	B. NMT (b) (4)%	B. 10-08-03-6654
(b) (4)	C. NMT (b) (4)%	C. 10-08-03-6654

Test	Acceptance Criteria	Test Method ¹
(b) (4)	D. NMT (b) (4)%	D. 10-08-03-6654
(b) (4)	E. NMT (b) (4)%	E. 10-08-03-6654
F. Any Other Individual Impurity	F. NMT (b) (4)%	F. 10-08-03-6654
G. Total Impurities	G. NMT (b) (4)%	G. 10-08-03-6654
Residual Solvents:	No other solvents, including those established per USP<467> as Class 1, 2 or 3 solvents, are likely to be present, per vendor's certification, except (b) (4)	USP<467>
(b) (4)	NMT (b) (4)%	USP <731>
Microbial Bioburden		
Total Yeast and Mold Count	NMT (b) (4)CFU/g	USP <61>
Total Aerobic Count	NMT (b) (4)CFU/g	
Bacterial Endotoxins	NMT (b) (4)EU/mg	USP <85>

¹ References to compendia signify current compendia. If a compendial monograph or test changes, APP will implement the changes and report them via annual report.

Drug Product:**Pharmaceutical Development:**

This drug product has been available in the market for over 40 years and follows the same formulation and controls as specified by USP monograph. The applicant has not provided any detailed developmental study for this NDA. The formulation contains a large quantity of phenol as preservative. The osmolality/isotonicity of the drug products has not been discussed. Osmolality and isotonicity are important safety attributes for the parenteral drug products. The review should incorporate these attributes and request information from the applicant. This is a review issue. No overages are reported in the manufacturing process. Each 10 mL vial is filled with 10 mL for both the proposed strengths.

Manufacturer & Manufacturing Process:

The manufacturer is APP Pharmaceuticals, Grand Island, NY facility. This facility has been flagged by the Office of Compliance for cGMP violations and has been recommended for a Warning Letter as of 10/17/2011 and 01/03/2012 based on the CMS information. The reviewer should be aware of this issue. The status can be viewed by using the following link:

<http://intranetapps.fda.gov/scripts/mpqa/profile.cfm?FEI=3001833549>

All manufacturing and testing facilities that are provided in the submission have been submitted for cGMP compliance in EES.

The applicant has proposed a batch size of (b) (4) to give (b) (4) vials of 10 mL each for both strengths. Total volume has been accounted for along with the reconciled amount that was not filled into vials. The drug product is (b) (4)

The manufacturing process is represented in a flow diagram as provided:

Figure 3.2.P.3.3- 1 Manufacturing Flow Diagram for Neostigmine Methylsulfate Injection, USP

(b) (4)



The formulation is represented in the following tables depicting the components and composition of each of the proposed strengths of drug product:

Table 3.2.P.1- 1 Component Composition per Unit Dose for Product Code 38210

Strength	0.5 mg/mL		
Packaging Configuration	10 mL fill in a 10-cc vial		
Vial	10 cc, Type I, (b) (4) Amber glass vial		
	(b) (4)		
	(b) (4)		
Neostigmine Methylsulfate Injection, USP, 0.5 mg/mL	Content (per mL)	Function	Quality of ingredient
Neostigmine Methylsulfate, USP	0.5 mg ¹	Active Ingredient	USP
Phenol (as Liquefied Phenol, USP)	4.5 mg ²	Preservative	USP
Sodium Acetate, USP (Trihydrate)	0.2 mg	(b) (4)	USP
Water for Injection, USP	Q.S. to 1 mL		USP
(b) (4)			
(b) (4) Acetic Acid, USP	As Needed	pH Adjuster	USP
Sodium Hydroxide, NF	As Needed	pH Adjuster	NF

¹ The theoretical amount of Neostigmine Methylsulfate, USP is (b) (4) mg per (b) (4) L batch

² The theoretical amount of Phenol is (b) (4) mg per (b) (4) L batch

3.2.P.1 Description and Composition of the Drug Product (Neostigmine Methylsulfate Injection, USP, 0.5 mg/mL and 1.0 mg/mL (b) (4))

Table 3.2.P.1- 2 Component Composition per Unit Dose for Product Code 38310

Strength	1.0 mg/mL		
Packaging Configuration	10 mL fill in a 10-cc vial		
Vial	10 cc, Type I, (b) (4) Amber glass vial		
	(b) (4)		
	(b) (4)		
Neostigmine Methylsulfate Injection, USP, 1.0 mg/mL	Content (per mL)	Function	Quality of ingredient
Neostigmine Methylsulfate, USP	1.0 mg ¹	Active Ingredient	USP
Phenol (as Liquefied Phenol, USP)	4.5 mg ²	Preservative	USP
Sodium Acetate, USP (Trihydrate)	0.2 mg	(b) (4)	USP
Water for Injection, USP	Q.S. to 1 mL		USP
(b) (4)			
(b) (4) Acetic Acid, USP	As Needed	pH Adjuster	USP
Sodium Hydroxide, NF	As Needed	pH Adjuster	NF

¹ The theoretical amount of Neostigmine Methylsulfate, USP is (b) (4) mg per (b) (4) L batch

² The theoretical amount of Phenol is (b) (4) mg per (b) (4) L batch

Drug Product Specifications:

The drug product specifications as provided are shown below:

Table 3.2.P.5.1- 1 Regulatory Specification for Neostigmine Methylsulfate Injection, USP, 0.5 mg/mL, Product Code 38210 and 1.0 mg/mL, Product Code 38310

Test	Acceptance Criteria	Test Method ¹
Visual Inspection		
1. Appearance	1. Solution in amber vial	Visual Examination
2. Clarity	2. Clear	
3. Particulate Matter	3. Essentially free from visible particulate matter	
4. Container/Closure	4. Container is intact	
5. Visual Color	5. Colorless	
Identification ² :		
1. USP	1. A Cherry-red color is produced on addition of Diazobenzenesulfonic Acid TS.	1. USP
2. HPLC	2. The retention time of the major peak in the chromatogram of the <i>Standard Preparation</i> (Rs) injected before the <i>Sample Preparation</i> (Ru) meets the following criteria: (b) (4)	2. 10-08-03-6654
pH	5.0 – 6.5	USP <791>
Volume check ²	Code 38210: NLT 10.0 mL Code 38310: NLT 10.0 mL	USP<1>
Instrumental Color (b) (4)	NMT (b) (4)	03-08-07-0057
Container/Closure Integrity Test (CCIT) ³ Wilcomat-Differential Pressure (DP) Test	Sample DP values are lower than the self test DP values	10-08-00-6031 10-08-00-6032

Test	Acceptance Criteria	Test Method ¹
Phenol Assay Label Claim 4.5 mg/mL	(b) (4)	10-08-03-6665
Neostigmine Methylsulfate HPLC Assay Code 38210: Label Claim 0.5 mg/mL Code 38310: Label Claim 1.0 mg/mL	90.0% - 110.0% of Label Claim	10-08-03-6654
Related Compounds:		
(b) (4)	1. NMT (b) (4)	10-08-03-6654
2. Any Other Individual Impurity	2. NMT (b) (4)	
3. Total Impurities	3. NMT (b) (4)	
Particulate Matter	For Particles (b) (4) NMT (b) (4) per container For Particles (b) (4) NMT (b) (4) per container	USP <788>
Sterility ²	Sterile	USP<71>
Bacterial Endotoxins	NMT (b) (4)EU/mg	USP <85>
Other Requirements ²	Meets the requirements of USP<1>	
Statement of Compliance to USP <467>	This finished drug product complies to the USP<467> General Chapter for Residual Solvents per Option1	

¹ References to compendia signify current compendia. If a compendial monograph or test changes, APP will implement the changes and report them via annual report.

² Release tests only

³ Container Closure Integrity Testing (CCIT) is not a release test. CCIT will only be performed at annual stability intervals in accordance with the FDA *Guidance for Industry: Container Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol of Sterile Products*, February 2008.

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA (ONDQA)**

Batch analysis data:

The applicant has provided batch data of two batches for each strength.

0.5 mg/mL	Batch # R341-001	Volume	(b) (4)
0.5 mg/mL	Batch # R341-007	Volume	(b) (4)
1.0 mg/mL	Batch # R341-003	Volume	(b) (4)
1.0 mg/mL	Batch # R341-009	Volume	(b) (4)

These exhibit batches produced for the stability studies of this drug product.

The proposed batch volume is (b) (4) and the exhibit batches are (b) (4) or (b) (4) the size.

Container Closure System:

The drug product will be filled in (b) (4) glass vials with (b) (4) rubber stoppers from (b) (4).
(b) (4) The extractable information for the stopper is included from (b) (4).

Any extractable and leachable data requirement is a review issue and should be assessed carefully since a large amount of phenol is being used in the formulation. It should be noted that there are many other parenteral formulations that have similar or higher amount of phenol. All relevant DMFs associated with the container closure system should be reviewed. Container closure integrity should also be assessed.

Stability:

The submission includes stability protocol and a summary of the stability data available for the exhibit batches. The data submitted is only for six months both under accelerated and real time conditions. The applicant has requested 24 month expiry dating period quoting OGD guidance to industry. This is a review and a policy issue that must be discussed with the management before granting an extended expiry dating period. If no data for the exhibit batches are available supporting data must be provided.

Labeling:

The applicant has provided draft package insert according the Structured Product Labeling under Physician's Labeling Rule. No carton container labeling has been included until this date. The CMC portion of the labeling both package insert, carton and container should be reviewed as and when received in the EDR.

Critical Issues and recommendations for review:

This initial quality assessment is an overview of what has been provided by the applicant in this submission and should not be construed as a complete assessment. During assessment of the CMC information provided in this NDA, the primary reviewer should consider addressing issues identified below, related issues and beyond. The reviewer is likely to find additional issues that are not covered here which may impact the quality of the drug product through its shelf-life.

- Drug Substance DMF # should be reviewed for adequacy.

File name: NDA 203-629-Product Quality Filing

Review.doc

Version Date: 05132009

Reference ID: 3090309

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA (ONDQA)

- Suitability of the drug product manufacturing process, which includes (b) (4) and (b) (4) should be assessed in consultation with the Microbiologist.
- Manufacturing process validation should be assessed.
- The manufacturing facility proposed for this drug product is recommended for a 'Warning Letter' by the Office of Compliance as of January, 2012 due to overall cGMP violations and the Quality Systems.
- Hold times of solutions during manufacturing process and conditions used in the finished product to assure sterility should be assessed.
- Osmolality/isotonicity of the drug product should be considered as these may impact safety.
- The formulation uses (b) (4) times the amount of phenol in 0.5 mg strength and (b) (4) times the amount of phenol in 1.0 mg strength. Appears to be a large amount of phenol used. This should be assessed for any safety or toxicity.
- Impurities in drug substance and drug products, their limits per ICHQ3B(R) based on toxicological assessment by the Pharmtox group. Note potential genotoxic impurities (b) (4)
- Extractable and leachable profiles and their limits in the drug product (during stability) from the container closure system in consultation with Pharmtox.
- Validation of the analytical methods.
- DMF of the container closure system should be reviewed as needed.
- The expiration dating period requested is based on the OGD guidance. The applicant's request for 24 month expiry dating based on six month stability data and should be evaluated per ICH Q1E guidance documents.
- Labeling – package insert has been provided in the latest amendment. (74 day letter)

Recommendation for Filing:

From CMC perspective this NDA is recommended to be filed for complete review.

Information request for the 74 day letter:

- 1. Provide carton container labels**
- 2. Provide Method validation package**

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA (ONDQA)

Team Review:

CMC review should communicate and co-ordinate relevant issues with Microbiology, Biopharmaceutics and Toxicology disciplines. The formulation does not contain novel excipients. The manufacturing process is simple and the dosage form is parenteral. The Office of Compliance should be consulted about the status of the facility from time to time during the review process.

Consults:

1. **Microbiology** (Assigned to Dr. Vinayak Pawar)
2. **Biopharmaceutics, ONDQA** (Assigned to Dr. Minerva Hughes)
3. **Toxicology** (Assigned to Dr. Huiqing Hao)

Ramesh Raghavachari, Ph.D.
CMC Lead

02/17/2012
Date

Prasad Peri, Ph.D.
Branch VIII Chief, ONDQA

02/17/2012
Date

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA (ONDQA)

NDA Number: 203-629
Neostigmine
Methylsulfate
Injection, USP
0.5 mg/mL
1.0 mg/mL

Supplement Number and Type: **Established/Proper Name:**
N.A. **Neostigmine Methylsulfate**

Letter Date: December 28, 2011 **Stamp Date: December 28, 2011**

Applicant:

APP
Pharmaceuticals Inc.

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	x		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA (ONDQA)**

4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	Review issue		
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B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		on form FDA 356h
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			Not applicable

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA (ONDQA)**

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	x		
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	x		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA (ONDQA)**

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	x		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	x		Form FDA 356h

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	x		Section 1.12.14

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA (ONDQA)**

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?		x	DMF # (b) (4) has been referenced.
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?		x	DMF # (b) (4) has been referenced
14.	Does the section contain information regarding the characterization of the DS?		x	DMF # (b) (4) has been referenced
15.	Does the section contain controls for the DS?		x	DMF # (b) (4) has been referenced
16.	Has stability data and analysis been provided for the drug substance?		x	DMF # (b) (4) has been referenced
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		x	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		x	not an approvability issue

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA (ONDQA)**

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	x		
21.	Is there a batch production record and a proposed master batch record?	x		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?		x	Not applicable- this is a marketed unapproved drug product
23.	Have any biowaivers been requested?	x		Biopharm reviewer will be reviewing this portion of the application
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	x		
25.	Does the section contain controls of the final drug product?	x		
26.	Has stability data and analysis been provided to support the requested expiration date?	x		Review issue
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		x	

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA (ONDQA)**

28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	not an approvability issue
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**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA (ONDQA)**

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?		x	Request will made in the 74 day letter.

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	x		

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	x		DMF references are provided, however, the review requirement of each DMF depends upon the information provided in the NDA.

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	II		(b) (4)	06/30/2011	(b) (4)
	III			07/07/2011	
	III			08/31/2011	
	III			08/12/2011	

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA (ONDQA)

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	x		
33.	Have the immediate container and carton labels been provided?		x	Request for carton and container labeling in the 74 day letter

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA (ONDQA)**

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	x		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?			None at this point.

{See appended electronic signature page}

Ramesh Raghavachari, Ph.D.
CMC Lead
Division of New Drug Quality
Assessment III
Office of New Drug Quality
Assessment

Date

{See appended electronic signature page}

Prasad Peri, Ph.D.
Chief, Branch VIII
Division of New Drug Quality
Assessment III
Office of New Drug Quality
Assessment

Date

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

/s/

RAMESH RAGHAVACHARI
02/21/2012
Filing review- IQA

PRASAD PERI
02/22/2012
I concur