

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206289Orig1s000

CHEMISTRY REVIEW(S)

NDA 206289

Atropine Sulfate Ophthalmic Solution, USP, 1%

Akorn, Inc.

Fuqiang Liu, Ph.D.

Branch V, ONDQA

For the Division of Transplant and Ophthalmology Products

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Chemistry Review Data Sheet

1. NDA 206289
2. REVIEW #: Addendum 1 to Review #1
3. REVIEW DATE: 11-Jul-2014
4. REVIEWER: Fuqiang Liu, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

None

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

SDN# 010 Quality/Response to Information Request
SDN# 013 Quality/Response to Information Request
SDN# 014 Quality/Response to Information Request

Document Date

09-Apr- 2014
19-May-2014
22-May-2014

7. NAME & ADDRESS OF APPLICANT:

Name: Akorn, Inc.
Address: 1925 West Field Court, Suite 300
Lake Forest, IL 60045
Representative: Sam Boddapati, Ph. D.
Telephone: (847) 353-4909

8. DRUG PRODUCT NAME/CODE/TYPE:

Chemistry Review Data Sheet

- a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Atropine Sulfate
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 7
 - Submission Priority: P

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

10. PHARMACOL. CATEGORY: For (b) (4)
mydriasis; for pupillary dilation (b) (4)

11. DOSAGE FORM: Solution/eye drops

12. STRENGTH/POTENCY: 1%

13. ROUTE OF ADMINISTRATION: Topical (ocular)

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

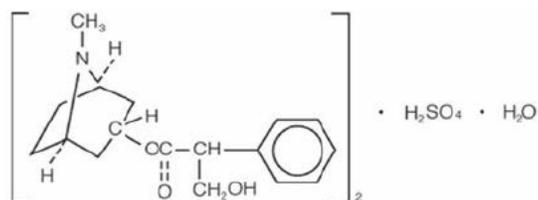
Not a SPOTS product

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

Chemical Name: USP Monograph: Atropine Sulfate
INN (modified): Atropine Sulphate monohydrate
Benzeneacetic acid, α -(hydroxymethyl)-, 8-methyl-8-azabicyclo[3,2,1]oct-3-yl ester, *endo*-(\pm)-, sulfate (2:1) (salt), monohydrate.
1 α H, 5 α H-Tropan-3- α -ol (\pm)-tropate (ester), sulfate (2:1) (salt) monohydrate.

Structural Formula:

Chemistry Review Data Sheet



Molecular Formula: $(C_{17}H_{23}NO_3)_2 \cdot H_2SO_4 \cdot H_2O$

Molecular mass: 694.83 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCE D	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate		Reviewed by (b) (4)
	III			3	Adequate		Reviewed by (b) (4)
	III			3	Adequate		Reviewed by (b) (4)
	III			3	Adequate		Reviewed by (b) (4)
	III			3	Adequate		Reviewed by (b) (4)
	III			3	Adequate		Reviewed by (b) (4)

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")

Chemistry Review Data Sheet

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
NDA	21146	Different formulation of the same drug (IV)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	26-Jun-2014	Linda Ng
Pharm/Tox	Approval	3-Apr-2014	Aaron Ruhland
Biopharm	Approval	26-Nov-2013	Elsbeth Chikhale
LNC	N/A		
Methods Validation	N/A		
OPDRA	N/A		
EA	Not required		
Microbiology	Approval	24-Feb-2014	Steven P. Donald

The Chemistry Review for NDA 206289

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 206289 provides adequate CMC information to assure the identity, strength, purity and quality of the drug product. The Drug Master File (DMF (b) (4) from (b) (4)) for atropine sulfate drug substance referenced for this NDA is adequate and supports this application. CMC related labeling comments have been shared with the review team and will be finalized during OND team label review. The overall recommendation from the Office of Compliance is “acceptable” as of June 26, 2014 for the establishment evaluation. Therefore, from the CMC perspective, NDA 206289 is recommended for approval at this time.

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

None

II. Summary of Chemistry Assessments

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

Drug Substance

The drug substance information is referenced to (b) (4) DMF (b) (4). A Letter of Authorization (LOA) to reference this DMF is provided. DMF (b) (4) which also currently supports NDA 21146 (atropine sulfate injection, USP, approved on December 2000) was found adequate to support the NDA under review. Since the last review of this DMF in 2009, there have been updates to the DMF via Annual Reports, and CMC amendments. Most of the changes are minor and editorial in nature. No substantial CMC changes were noted in these submissions. Most recently, (b) (4) (b) (4) updated the DMF on November 2013 to align the specification to the current USP monograph which became effective August 1, 2013. Batch analysis of all four batches of the drug substance used by Akorn complied with the current drug substance specification. Therefore, DMF (b) (4) is adequate to support NDA 206289.

Drug Product

Atropine Sulfate Ophthalmic solution, USP, 1%, is a sterile, (b) (4) and preserved aqueous solution formulated for topical application. Each milliliter of Atropine Sulfate

Executive Summary Section

Ophthalmic Solution, USP, 1%, contains atropine sulfate (b) (4) USP, 1% (10 mg/mL) and the following inactives: Hypromellose (b) (4) (2910), Dibasic Sodium Phosphate (b) (4), Monobasic Sodium Phosphate (b) (4), Edetate Disodium, Water for Injection, Hydrochloric Acid and/or Sodium Hydroxide to adjust the pH. Benzalkonium Chloride, 0.01% (0.1 mg/mL) is used as preservative. All excipients are compendial.

The drug product manufacturing process involves (b) (4). Atropine Sulfate Ophthalmic Solution, USP, 1%, is supplied in 2 mL, 5 mL, and 15 mL fill sizes. In support of this NDA application, nine exhibit batches of Atropine Sulfate Ophthalmic Solution, USP, 1%, in 2 mL, 5 mL and 15 mL fill sizes were manufactured and also used in the stability studies to establish expiration date. The sterile (b) (4) solution has an osmolality of 260-320 mOsm/kg and a pH of 3.5-6.0. Drug product specification include tests for identification, atropine sulfate assay, impurities, assay for EDTA and benzalkonium chloride, and physical measurements, e.g., particulates, appearance (color, clarity) etc. The specification also includes microbiological, sterility and container closure integrity tests. Atropine Sulfate Ophthalmic Solution, USP, 1%, has acceptable stability for at least 18 months for all three configuration sizes (2 mL in 6 mL bottle, 5 mL in 6 mL bottle and 15 mL in 15 mL bottle) when stored at 25°C ± 2 °C.

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

Atropine sulfate is an anti-muscarinic agent indicated for cycloplegia and/or mydriasis. It can also be used for pupillary dilation (b) (4). The recommended dosage is (b) (4). The drug product (Atropine Sulfate Ophthalmic solution, USP, 1%) is a sterile, (b) (4) and preserved aqueous solution of atropine sulfate. The drug product is supplied as 2 mL solution in a 6 mL bottle, 5 mL solution in a 6 mL bottle and 15 mL solution in a 15 mL bottle. The recommended storage is, "Store at 20 °C - 25 °C (68 °F - 77 °F)" in a tightly closed container. Based on evaluation of the stability data presented, the recommended expiration date is 18 months.

C. Basis for Approvability or Not-Approval Recommendation

The drug substance information is adequately supported by DMF (b) (4). Information provided regarding drug product manufacturing, raw materials controls and specifications, analytical methods, and drug product stability is adequate to support the quality of the drug product through the recommended shelf-life of 18 months.

Finalizing labeling is pending OND team review. The overall recommendation from the Office of Compliance is acceptable as of June 26, 2014 for the establishment evaluation. Therefore, NDA 206289 is recommended for approval from CMC perspective.

Executive Summary Section

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

Fuqiang Liu, Ph.D.

B. Endorsement Block

Balajee Shanmugam, Ph. D.
CMC Lead

Rapti Madurawe, Ph.D.
Branch chief

C. CC Block

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/s/

FUQIANG P LIU
07/14/2014

BALAJEE SHANMUGAM
07/14/2014

RAPTI D MADURawe
07/14/2014

NDA 206289

Atropine Sulfate Ophthalmic Solution USP, 1%

Akorn, Inc.

**Fuqiang Liu, Ph.D.
Branch V, ONDQA**

For the Division of Transplant and Ophthalmology Products

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Chemistry Review Data Sheet

1. NDA 206289
2. REVIEW #: 1
3. REVIEW DATE: 3-Apr-2014
4. REVIEWER: Fuqiang Liu, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original NDA	23-Oct- 2013
SDN# 004 Quality/Quality Information	12-Nov-2013
SDN# 005 Quality/Response to Information Request	03-Dec-2013
SDN# 007 Quality/Microbiology Information	10-Jan-2014
SDN# 008 Quality/Response to Information Request	14-Feb-2014
SDN# 009 Quality/Response to Information Request	21-Mar-2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Akorn, Inc.
Address:	1925 West Field Court, Suite 300 Lake Forest, IL 60045

Chemistry Review Data Sheet

Representative: Sam Boddapati, Ph. D.

Telephone: (847) 353-4909

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: None
- b) Non-Proprietary Name (USAN): Atropine Sulfate
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 7
 - Submission Priority: P

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

10. PHARMACOL. CATEGORY: For (b) (4)
mydriasis; for pupillary dilation (b) (4)

11. DOSAGE FORM: Solution/eye drops

12. STRENGTH/POTENCY: 1%

13. ROUTE OF ADMINISTRATION: Topical (ocular)

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): SPOTS product – Form Completed Not a SPOTS product

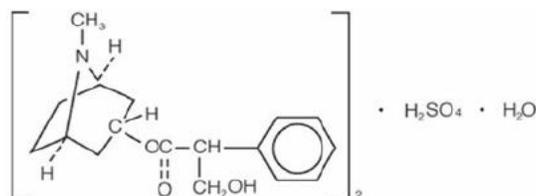
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: USP Monograph: Atropine Sulfate

Chemistry Review Data Sheet

INN (modified): Atropine Sulphate monohydrate
 Benzeneacetic acid, α -(hydroxymethyl)-, 8-methyl-8-azabicyclo[3,2,1]oct-3-yl ester, *endo*-(\pm)-, sulfate (2:1) (salt), monohydrate.
 1 α H, 5 α H-Tropan-3- α -ol (\pm)-tropate (ester), sulfate (2:1) (salt) monohydrate.

Structural Formula:


 Molecular Formula: $(C_{17}H_{23}NO_3)_2 \cdot H_2SO_4 \cdot H_2O$

Molecular mass: 694.83 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCE D	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1,3	Adequate		Reviewed by (b) (4)
	III			3	Adequate		Reviewed by (b) (4)
	III			3	Adequate		Reviewed by (b) (4)
	III			3	Adequate		Reviewed by (b) (4)
	III			3	Adequate		Reviewed by (b) (4)
	III			3	Adequate		Reviewed by (b) (4)

¹ Action codes for DMF Table:

1 – DMF Reviewed.

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

Chemistry Review Data Sheet

- 2 – Type 1 DMF
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- 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
NDA	21146	Different formulation of the same drug (IV)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	pending		
Pharm/Tox	pending		
Biopharm	Approval	26-Nov-2013	Dr. Elsbeth Chikhale
LNC	N/A		
Methods Validation	N/A		
OPDRA	N/A		
EA	Not required		
Microbiology	Approval	24-Feb-2014	Steven P. Donald

The Chemistry Review for NDA 206289

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 206289 provides adequate CMC information to assure the identity, strength, purity and quality of the drug product. The Drug Master File (DMF (b) (4) from (b) (4) for atropine sulfate drug substance referenced for this NDA is adequate and supports this application. Revisions to the CMC sections of the labels and labeling will be finalized during OND team review. The inspection of Akorn drug product facility is tentatively scheduled for April 28-May 9, 2014 which falls after the PDUFA date and therefore as of April 1, 2014, the status of overall recommendation from the Office of Compliance is PENDING. Therefore, from CMC perspective, approval of this NDA remains contingent upon an overall recommendation of "acceptable" in EES and acceptability of the final labeling; for the above mentioned reasons, a recommendation for approval is not made at this time.

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

None

II. Summary of Chemistry Assessments

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

Drug Substance

The drug substance information is referenced to (b) (4) DMF (b) (4) A Letter of Authorization (LOA) to reference this DMF is provided. DMF (b) (4) which also currently supports NDA 21146 (atropine sulfate injection, USP, approved on December 2000) was found adequate to support the NDA under review. Since the last review of this DMF in 2009, there have been updates to the DMF via Annual Reports, and CMC amendments. Most of the changes are minor and editorial in nature. No substantial CMC changes were noted. Most recently, (b) (4) updated the DMF on November 2013 to update the specification to align with the current USP monograph which became effective August 1, 2013. Batch analysis of all four batches of the drug substance used by Akorn complied with the current drug substance specification. Therefore, DMF (b) (4) is adequate to support NDA 206289.

Drug Product

Executive Summary Section

Atropine Sulfate Ophthalmic solution USP, 1% is a sterile, (b) (4) and preserved aqueous solution formulated for topical application. Each milliliter of Atropine Sulfate Ophthalmic Solution USP, 1% contains atropine sulfate (b) (4) USP, 1% (10 mg/mL) and the following inactives: Hypromellose (b) (4) (2910), Dibasic Sodium Phosphate (b) (4), Monobasic Sodium Phosphate (b) (4), Edetate Disodium, Water for Injection, Hydrochloric Acid and/or Sodium Hydroxide to adjust the pH. Benzalkonium Chloride, 0.01% (0.1 mg/mL) is used as preservative. All excipients are compendial.

The drug product manufacturing process involves (b) (4) (b) (4) Atropine Sulfate Ophthalmic Solution USP, 1% is supplied in 2 mL, 5 mL, and 15 mL fill sizes. In support of this NDA application, nine exhibit batches of Atropine Sulfate Ophthalmic Solution USP, 1%, in 2 mL, 5mL and 15 mL fill sizes were manufactured and also used in the stability studies to establish expiration date. The sterile (b) (4) solution has an osmolality of 260-320 mOsm/kg and a pH of 3.5-6.0. Drug product specification include tests for identification, atropine sulfate assay, impurities, assay for EDTA and benzalkonium chloride, and physical measurements, e.g., particulates, appearance (color, clarity) etc. The specification also includes microbiological tests, sterility and container closure integrity. Atropine Sulfate Ophthalmic Solution USP, 1%, has acceptable stability for at least 18 months for all three configuration sizes (2 mL in 6 mL bottle, 5 mL in 6 mL bottle and 15 mL in 15 mL bottle) when stored at 25°C ± 2 °C.

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

Atropine sulfate is an anti-muscarinic agent indicated for cycloplegia and/or mydriasis. It can also be used for pupillary dilation (b) (4). The recommended dosage is (b) (4). The drug product (Atropine Sulfate Ophthalmic solution USP, 1%) is a sterile, (b) (4) and preserved aqueous solution of Atropine sulfate. The drug product is supplied as 2 mL solution in a 6 mL bottle, 5 mL solution in a 6 mL bottle and 15 mL solution in a 15 mL bottle. The recommended storage is, "Store at 20 °C - 25 °C (68 °F - 77 °F)" in a tightly closed container. Based on evaluation of the stability data presented, the recommended expiration date is 18 months.

C. Basis for Approvability or Not-Approval Recommendation

The drug substance information is adequately supported by DMF (b) (4) Information provided regarding drug product manufacturing, raw materials controls and specifications, analytical methods, and drug product stability is adequate to support the quality of the drug product through the recommended shelf-life of 18 months.

Executive Summary Section

Labels and labeling are pending final OND team review. Revisions to the CMC sections of the labels and labeling are marked up and will be finalized during team review.

As of April 1, 2014, the overall recommendation for the manufacturing and testing facilities is PENDING.

Approval of this NDA is contingent upon an overall recommendation of "acceptable" of all facilities from OC and the acceptability of the final labeling. Therefore, at this time, this NDA is not recommended for approval.

III. Administrative

A. Reviewer's Signature

Fuqiang Liu, Ph.D.

B. Endorsement Block

Balajee Shanmugam, Ph. D.
CMC Lead

Rapti Madurawe, Ph.D.
Branch chief

C. CC Block

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/s/

FUQIANG P LIU
04/04/2014

BALAJEE SHANMUGAM
04/04/2014

RAPTI D MADURawe
04/04/2014

Initial Quality Assessment (IQA) and Filing Review for Pre-Marketing Applications

Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: **206289**

2. DATES AND GOALS:

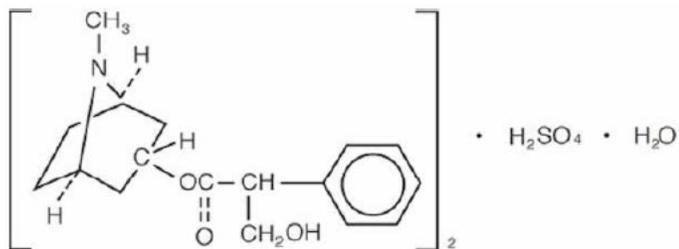
Letter Date: October 22, 2013	Submission Received Date : October 30, 2013
PDUFA Goal Date: April 30, 2014	

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	None proposed
Established or Non-Proprietary Name (USAN):	Atropine sulfate
Dosage Form:	Ophthalmic Solution
Route of Administration	Topical ocular
Strength/Potency	1%
Rx/OTC Dispensed:	Rx

4. INDICATION: (b) (4) mydriasis and for pupillary dilation.

5. DRUG SUBSTANCE STRUCTURAL FORMULA:



6. NAME OF APPLICANT (as indicated on Form 356h): Akorn

**ONDQA - Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications
(CMC and Biopharmaceuticals)**

7. SUBMISSION PROPERTIES:

Review Priority:	Priority
Submission Classification (Chemical Classification Code):	7
Application Type:	505(b)(2)
Breakthrough Therapy	No
Responsible Organization (Clinical Division):	DTOP
Orphan Designation	No
Combination Product	No

8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics			
Clinical Pharmacology			
Establishment Evaluation Request (EER)	x		
Pharmacology/Toxicology			
Methods Validation	x		Recommend submitting for MV (b) (4)
Environmental Assessment			
CDRH			
Other			

**ONDQA - Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications
(CMC and Biopharmaceutics)**

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective? Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>
CMC Filing Issues: None

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter? Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>
CMC Comments for 74-Day Letter: None

Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective? Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>
Biopharmaceutics Filing Issues:

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter? Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>
Biopharmaceutics Comments for 74-Day Letter:

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective? Yes <input type="checkbox"/> No <input type="checkbox"/>
Microbiology Filing Issues: See Microbiology Filing Review for details and for any potential Microbiology review issues.

**ONDQA - Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications
(CMC and Biopharmaceuticals)**

Summary of Initial Quality Assessment

Does the submission contain any of the following elements? No			
Nanotechnology	QbD Elements	PET	Other, please explain
x	x	x	

Is a team review recommended?	Yes	No
Suggested expertise for team:		

Review Team Assignments (if known)	
Product Quality	Fuqiang Liu
Biopharmaceuticals	Elsbeth Chikhale
Product Quality Microbiology	Steven Donald
ONDQA PM	Navdeep Bhandari

CMC Summary of Critical Issues and Complexities:

The NDA provides for atropine sulfate ophthalmic solution USP, 1%. The drug product is currently being marketed under Grandfather status without FDA approval.

The two main issues identified during the initial evaluation of the NDA are:

- Impurities in drug product:** (b) (4) appears to be the only impurity tested in the drug product but recently Akorn revised the drug product specification and stability protocol to include tests for two additional impurities, (b) (4). It is not clear if all batches manufactured thus far showed only (b) (4) and not the other impurities; batch analysis offers no information on the presence or absence of the other two impurities. A review of the analytical method for impurity may offer some insight to the impurity profile across batches. (b) (4)

Akorn decided to add tests for the other impurities, most likely as a precautionary measure. As an assessment of the impurities section of the NDA is undertaken, the following questions should be considered: *Did any batch have either one or all of the newly added impurities, if it did what were the levels and why were the stability batches not tested for these impurities? If these impurities were not detected, is it due to the limitation of the analytical method to detect these impurities or is it possible that these impurities do not arise in Akorn's product? If the later is true, if none of the batches indicated the presence of the newly added impurities, what is the rationale for Akorn to include them and what safety risk does it pose by not including them? Alternatively, can the test for impurities be retained in the current review cycle and as Akorn generates more data can an evaluation be done at that point to determine whether or not to continue the tests? Could this be addressed by a Post-Marketing Commitment? Is the analytical method robust enough to detect the newly added impurities? Is the method fully and adequately validated? The validation of the methods needs to be reviewed carefully and a methods validation*

**ONDQA - Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications
(CMC and Biopharmaceutics)**

request to (b) (4) should be considered. Since the inclusion of the additional tests, has any batch been reanalyzed for the added impurities? What does the impurity profile look like? How is the proposed acceptance levels justified (see below)? Should we request for an update before mid-cycle on any reanalyzed batches?

- 2. Drug Product Specification:** *There are several issues associated with drug product specification (such as including tests which may be redundant, incomplete information etc.) which needs careful evaluation. Please see discussion below for details.*

The CMC information for the drug substance, atropine sulfate is referenced (b) (4) which has been previously reviewed (please see IQA below for details on the status).

The drug product is formulated as a (b) (4), preserved and sterile solution for topical use. No novel excipients are used. There is adequate stability data to evaluate the quality attributes over the intended shelf-life.

**ONDQA - Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications
(CMC and Biopharmaceutics)
Initial Quality Assessment**

The NDA provides for atropine sulfate ophthalmic solution, 1 % which is a currently marketed but unapproved product. The drug product is formulated as a (b) (4) sterile, preserved solution for topical ophthalmic use.

Drug Substance

- The drug substance has been referenced to (b) (4). The last review by Yong Hu, dated June 30, 2009 for an IND found it adequate but had sent an IR. The IR response, a few quality amendments and annual reports will require review. Note that the above review mentions that an earlier review of the DMF dated October 12, 2000 for a NDA found the DMF to be adequate. However, this review could not be located in DARRTS but a hard copy may be filed with the DMF. Please check to see what the incoming API's acceptance criteria and its adequacy.

Drug Product

- The drug product is formulated as a sterile, preserved solution and presented in the following configurations: 6mL bottle with 2mL and 5 mL fill volumes; 15 mL bottle with 15 mL fill volume. *A perusal of the stability data shows no noticeable differences between them but needs to be verified,* (b) (4)
- *The pH of the formulation is adjusted to keep it between 3.5 and 6.0.* (b) (4)
Please check with clinical if the proposed pH range is optimal/acceptable.
- (b) (4)
- *As mentioned above, Akorn recently revised the specification to include tests for additional impurities. It is likely that these impurities were never observed or tested for. Given this possibility, how did Akorn come up with the proposed acceptance levels for these impurities and how is it justified? What data are these levels based off? Any available data should be submitted for our evaluation. The proposed total impurity is (b) (4) % which again does not seem to be justified;* (b) (4)
Note that the proposed acceptance values for release and stability for a few quality attributes (such as assay) are different. In assessing the adequacy of the proposed specification, consider evaluating the need for the included tests such as assay for EDTA. It appears that particulate matter is tested per USP but it does not specifically state if the batches are tested for (b) (4)

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(b) (4)

- *The DP specification includes test for sterility and container closure integrity. Consult with Micro reviewer if both tests are required or if any one will be adequate.*
- *With regards drug product stability, data on long-term stability for the primary batches for all three configurations has been provided. However, the accelerated stability data is limited to only 3-months for all batches. Akorn indicates that they will submit updated accelerated stability data for at least one batch during the review cycle. An early IR should be considered to address this and other observations regarding DP specification.*
- *Also, no data has been provided on the stability samples for attributes such preservative effectiveness, viscosity etc. These issues should be addressed by following up with Akorn.*
- *Based on the data from three primary stability batches and supportive stability for the three fill volumes, an expiration dating of (b) (4) months is requested.*
- *The NDA provides information on extractables and leachables in Section 3.2.P.7. Please consult with Pharm/Tox on the adequacy of the proposed qualification threshold of (b) (4) for identification, quantification, and qualification. Chromatogram traces have been provided although a tabular representation of the compounds and the level present would have been helpful. This could be another potential IR.*
- *Please verify if the NDA provides data on drop volume.*

Labeling:

The container and carton label for the 6 ml configuration for the two fill volumes of 2 mL and 5 mL seems visually indistinguishable. DMEPA may recommend highlighting the fill volume or use colored font to make the two fill volumes distinct. Consider bringing this up with clinical and DMEPA if this not brought up by any of them. This is not anticipated to cause medication error to be a safety issue.

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Biopharmaceutics Assessment

Biopharmaceutics Critical Issues or Complexities

The Applicant is seeking approval for a New Drug Application (NDA) for Atropine Sulfate Ophthalmic Solution, 1% under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The proposed indication is for the treatment of [REDACTED] ^{(b) (4)} mydriasis and for pupillary dilation. The Applicant has been marketing Atropine Sulfate Ophthalmic Solution USP, 1% under "Grandfather" status since June 19, 1995. This NDA relies on published literature for clinical and non-clinical information. Since there is no approved NDA or ANDA for Atropine Sulfate Ophthalmic Solution, 1%, a waiver of the requirement to submit in vivo bioequivalence/bioavailability is not applicable. Instead, the Applicant has provided the pharmacokinetic (PK) information by reference to the published literature. The acceptability of these PK data will be determined by the Clinical Pharmacology Reviewer.

This NDA does not require further assessment from the ONDQA-Biopharmaceutics team. Therefore, this filing review concludes the Biopharmaceutics involvement on this NDA.

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FILING REVIEW CHECKLIST

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		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?			NA

B. FACILITIES*				
* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a <i>potential filing issue</i> or a <i>potential review issue</i> .				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		
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.			

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	Parameter	Yes	No	Comment
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 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		

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	Parameter	Yes	No	Comment
9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <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		

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

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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		DS from (b) (4) is referenced to DMF (b) (4) and a LOA has been submitted.
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?			See above
14.	Does the section contain information regarding the characterization of the DS?			See above
15.	Does the section contain controls for the DS?			
16.	Has stability data and analysis been provided for the drug substance?			
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	

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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		
23.				
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		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		x	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	x		

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G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product	x		
H. DEVICE				
	Parameter	Yes	No	Comment
31.	If appropriate, is there a section providing information on the device		x	

I. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
32.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	x		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	(b) (4)	
(b) (4)	III	(b) (4)	(b) (4)	(b) (4)	
(b) (4)	III	(b) (4)	(b) (4)	(b) (4)	
(b) (4)	III	(b) (4)	(b) (4)	(b) (4)	
(b) (4)	III	(b) (4)	(b) (4)	(b) (4)	
(b) (4)		(b) (4)	(b) (4)	(b) (4)	

J. LABELING				
	Parameter	Yes	No	Comment
33.	Has the draft package insert been provided?	x		
34.	Have the immediate container and carton labels been provided?	x		

K. BIOPHARMACEUTICS				
	Parameter	Yes	No	Comment
35.	Does the application contain dissolution data?		x	The proposed dosage form is a solution.
36.	Is the dissolution test part of the DP specifications?			N/A
37.	Does the application contain the dissolution method development report?			N/A

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38.	Is there a validation package for the analytical method and dissolution methodology?			N/A
39.	Does the application include a biowaiver request?	x		Since there is no approved NDA or ANDA for Atropine Sulfate Ophthalmic Solution, 1%, a waiver of the requirement to submit in vivo bioequivalence/bioavailability is not applicable.
40.	Does the application include an IVIVC model?			N/A
41.	Is information such as BCS classification mentioned, and supportive data provided?			N/A
42.	Is information on mixing the product with foods or liquids included?			N/A
43.	Is there any in vivo BA or BE information in the submission?			Absolute BA data from published literature studies (Kaila et al.) are provided in the NDA. These data will be reviewed by the Clinical Pharmacology Reviewer.
FILING CONCLUSION				
	Parameter	Yes	No	Comment
44.	ARE THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	x		
45.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			N/A
46.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			N/A
47.	Are there any potential review issues identified?		x	

**ONDQA - Initial Quality Assessment (IQA) and Filing Review
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REVIEW AND APPROVAL

This document will be sequentially signed in DARRTS by all of the following who authored or reviewed this assessment:

[See appended electronic signature page](#)

Balajee Shanmugam, Ph.D.

CMC-Lead

Division

Office of New Drug Quality Assessment

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Elsbeth Chikhale, Ph.D.

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Rapti Madurawe, Ph.D.

Branch Chief

Division

Office of New Drug Quality Assessment

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

/s/

BALAJEE SHANMUGAM
11/26/2013

ELSBETH G CHIKHALE
11/26/2013

SANDRA SUAREZ
11/26/2013

RAPTI D MADURAWA
11/26/2013

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

Application: NDA 206289/000
Org. Code: 590
Priority: 7
Stamp Date: 23-OCT-2013
PDUFA Date: 30-APR-2014
Action Goal:
District Goal: 01-MAR-2014

Sponsor: AKORN
 1925 WEST FIELD CT STE 300
 LAKE FOREST, IL 60045
Brand Name: ATROPINE SULFATE OPHTHALMIC SOLUTION
 1%
Estab. Name:
Generic Name: ATROPINE SULFATE OPHTHALMIC SOLUTION
 1%
Product Number; Dosage Form; Ingredient; Strengths
 001; SOLUTION/DROPS; ATROPINE SULFATE; 1%

FDA Contacts:	F. LIU	Prod Qual Reviewer	3017961469
	S. DONALD	Micro Reviewer	(HFD-805) 4107795444
	O. SIMAKOVA	Product Quality PM	2404023814
	C. MARSHALL	Regulatory Project Mgr	3017963099

Overall Recommendation: ACCEPTABLE on 26-JUN-2014 by R. WITTORF () 2404023113
 PENDING on 11-APR-2014 by EES_PROD

Establishment: **CFN:** 1450114 **FEI:** 1450114
 AKORN, INC.

DECATUR, , UNITED STATES 625221412

Drug Name: **AADA:**

Capabilities: DRUG SUBSTANCE OTHER TESTER
 FINISHED DOSAGE LABELER
 FINISHED DOSAGE MANUFACTURER
 FINISHED DOSAGE OTHER TESTER
 FINISHED DOSAGE PACKAGER
 FINISHED DOSAGE RELEASE TESTER
 FINISHED DOSAGE STABILITY TESTER

Profile: (b) (4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 26-JUN-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)
DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER
Profile: NON-STERILE API BY CHEMICAL SYNTHESIS OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 05-JUN-2014
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)
DMF No: AADA:
Responsibilities: DRUG SUBSTANCE OTHER TESTER
FINISHED DOSAGE MANUFACTURER
CONTROL TESTING LABORATORY OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 28-MAY-2014
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

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

/s/

MARY GRACE LUBAO
08/28/2014