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RESEARCH**

APPLICATION NUMBER:

022305Orig1s000

CHEMISTRY REVIEW(S)

NDA 22-305

Pur-Wash (Purified Water 98.3%) Ophthalmic Solution

Niagara Pharmaceuticals

Muthukumar Ramaswamy, Ph.D.
Division of Non-Prescription Products and Clinical Evaluation (DNCE)

Table of Contents

Chemistry Review Data Sheet.....	3
The Executive Summary	6
I. Recommendations	6
A. Recommendation and Conclusion on Approvability:.....	6
Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable : none.....	6
II. Summary of Chemistry Assessments.....	6
A. Description of the Drug Product(s) and Drug Substance(s)	6
B. Description of How the Drug Product is Intended to be Used.....	6
C. Basis for Approvability or Not-Approval Recommendation.....	6
III. Administrative.....	8
A. Reviewer's Signature.....	8
B. Endorsement Block.....	8
C. CC Block	8
Chemistry Assessment	9
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	9
S DRUG SUBSTANCE.....	9
P DRUG PRODUCT	11
A APPENDICES	26
R REGIONAL INFORMATION	26
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	26
A. Labeling & Package Insert: Labeling review is in progress.....	26
Environmental Assessment Or Claim Of Categorical Exclusion:.....	27

Executive Summary Section

Chemistry Review Data Sheet

1. NDA 22305

2. REVIEW #: 2

3. REVIEW DATE: 06-30-11

4. REVIEWER: Muthukumar Ramaswamy, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Initial Quality Assessment (CMC) in DARRTS	4/17/2008
Refuse to file letter in DARRTS	4/25/2008
Initial Quality Assessment (CMC) in DARRTS	12/10/2010
Filing Communication (Filing issues Identified) in DARRTS	1/07/2011
PIND Meeting correspondence	09/6/2007

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original application	11/01/10
Amendment	11/30/10, 3/15/11, 4/18/11, 5/9/11 & 5/27/11, 5/31/11

7. NAME & ADDRESS OF APPLICANT:

Name:	Niagara Pharmaceuticals, Inc
Address:	60 INNOVATION DR , FLAMBOROUGH, ONTARIO, CA L9H 7P3
Representative:	R. Schiff
Telephone:	973-227-1830

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: Pur-Wash

Non-Proprietary Name (USAN): Purified water, 98.3% Code Name/# (ONDC only):

1. Chem. Type/Submission Priority (ONDC only):

- Chem. Type: Type 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)
10. PHARMACOL. CATEGORY: To Flush eyes of foreign objects
11. DOSAGE FORM: Solution
12. STRENGTH/POTENCY: 98.3%
13. ROUTE OF ADMINISTRATION: Topical

Executive Summary Section

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: Purified Water

Molecular weight: 18

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	1,4	N/A	5/11/11	LOA Letter dated august 21, 2009; Reviewed by M. Ramaswamy dated 5/11/11
	III			1	Adequate	5/24/2008	LOA Letter dated 0Aug. 18, 2009. Reviewed by R. Agarwal dated 5/24/2008.
	III			4	N/A	5/6/11	LOA Letter dated July 7, 2008. Reviewed by M. Ramaswamy dated 5/6/11
	III			1,4	Adequate	09/18/2000	LOA Letter dated Aug. 19, 2009. The last review of this DMF for (b) (4) review #8 M. J. Sloan 18-sep-2000) was found to be adequate.
	III			1,4	Adequate	7/16/2004	LOA Letter dated May 4, 2010. (b) (4) Reviewed by Li Shan Hsieh on 7/16/2004. (b) (4) meets the regulation in 21CFR.176.170(c)
	III			1,4	Adequate	09/07/10	DMF was reviewed by A. Banerjee on 09/07/10

¹ Action codes for DMF Table: <http://darrts.fda.gov:7777/darrts/ViewDocument?documentId=090140af801b3f2c>

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:

18. STATUS:



CHEMISTRY REVIEW



Executive Summary Section

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Adequate	1/18/11	Not Applicable (NA)
Pharm./Tox.	Adequate	6/7/11	Wafa Harrouk
Microbiology	Review pending	TBD	Denise Miller

Executive Summary Section

The Chemistry Review for NDA 22305

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability:

From CMC perspective, the NDA 22305 is recommended for approval pending acceptable recommendation from microbiology review.

A shelf-life of 24 months is recommended for the *storage of the proposed product under USP controlled room temperature (20° to 25° C (68° to 77°F))*.

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)

The proposed eye wash product is an isotonic, sterile aqueous solution. It contains (b) (4) boric acid (b) (4) sodium borate (b) (4) sodium chloride (b) (4) and purified water as active ingredient. The eye wash solution is packaged in 1-32 oz size HDPE container with appropriate type (b) (4) closure and tamper evident seal. The 1 and 4 oz bottles are provided with (b) (4) natural dropper tip and extended tip cap. Both 8 oz (b) (4) round and 16 oz cylindrical bottles are provided with a natural plug containing an orifice and a white cap. The 16 and 32 oz (b) (4) round bottles are provided with (b) (4) cap (closure with sealing gasket) and eye cup. The proposed product is for single-use only. The packaged product is (b) (4).

Component (SKU)	Description	Apparatus
1 oz (30 mL) (b) (4) round bottle	1 oz White HDPE (b) (4) Round	1 oz natural dropper tip (i.e. "nozzle equivalent")
4 oz (115 mL) (b) (4) round bottle	4 oz White HDPE (b) (4) Round	4oz natural dropper tip (i.e. "nozzle equivalent")
8 oz (225-250 mL) (b) (4) round bottle	8 oz White HDPE (b) (4) Round	8 oz natural plug (i.e. "nozzle equivalent")
16 oz (450-500 mL) Cylinder bottle	16 oz White HDPE cylinder Bottle	16 oz natural plug (i.e. "nozzle equivalent")
16 oz (450-500 mL) (b) (4) round bottle	16 oz White HDPE (b) (4) Round	Sterile eyecup
32 oz (900 mL-1L) (b) (4) round bottle	32 oz White HDPE (b) (4) Round	Sterile eyecup

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

The eye wash solution is proposed for cleansing the eye to help relieve irritation, (b) (4) burning, (b) (4) by removing loose foreign material, (b) (4)

The proposed product is for single-use only. Flush the affected eye as needed, controlling the rate of flow of solution by pressure on the bottle.

C. Basis for Approvability or Not-Approval Recommendation

The NDA is approvable pending satisfactory recommendation from microbiology review for the sterilization of eye wash and eye cup provided with 16 and 32oz bottles.

The NDA contains CMC information for a single-use only sterile eye wash solution packaged in 1-32 oz HDPE bottles. The containers are provided with appropriate type closure and tamper evident seal. The eye wash solution contains (b) (4) boric acid and (b) (4) sodium borate (b) (4) sodium chloride (b) (4), and purified water as active ingredient. The proposed drug product meets the definition of eye wash product proposed under CFR 349.20.

Executive Summary Section

The inactive ingredients in the drug product are compendial grade excipients and the proposed specification for these ingredients meet USP/NF monograph specifications. The active ingredient (purified water) is manufactured using a qualified water purification system and is produced on-demand to meet the drug product manufacturing needs. The proposed specification for the active ingredient includes (b) (4) conductivity, endotoxin content, total aerobic count, and absence of coli forms and meets the USP monograph requirements for purified water. Storage stability data is not needed for the purified water, as the water purification system generates purified water on demand.

The NDA contains adequate information on the composition, method of manufacture, in-process controls, test methods, and specification for the proposed drug product. The manufacturing process for the drug product involves (b) (4) filled in 1-32 oz size HDPE containers and capped with appropriate type (b) (4) closures and tamper evident (b) (4) seals in a packaging line.

(b) (4)

(b) (4)

The NDA contains adequate in-process controls for bulk eye wash manufacturing, filling and packaging operations. The proposed final specification for the product meets the USP monograph specification for eye wash solution. The finished product is tested for various physical and chemical attributes (appearance, color, assay of sodium chloride and boric acid, osmolality, heavy metals, specific gravity, particulate matter); microbiological attributes (sterility and endotoxin), and packaging integrity. The NDA contains acceptable method validation for the assay used for the determination of borate and chloride content.

The NDA contains information on the batch record used to manufacture the stability batches and also contains process validation data (bulk solution manufacturing, filling, capping, labeling and sterilization) to support the manufacturing of the proposed eye wash product. The NDA contains batch results for three stability batches and the test results for these batches met the proposed product release specification. The Firm uses USP certified reference standards (b) (4) for testing Purified Water.

The NDA contains information on specification, material of construction, and engineering drawings for packaging components. The Applicant has also provided appropriate reference to the DMFs associated with the packaging components. The Firm uses 1-32 oz high density polyethylene resin (HDPE) containers and (b) (4) closures for packaging the eye wash product. (b) (4) components meet regulations for food contact materials (21 CFR 177 (b) (4)). The Firm provided data for the proposed container which meet USP <661>/<671> test requirements.

The Firm has also completed a leachable assessment for the drug product stored under accelerated storage conditions (40°C ± 2°C at 75% RH ± 5%) for 6 months. The target leachables were present in these solutions at below detection limits. The Applicant provided adequate method validation information for the GC/MS method used for detecting leachables. The Firm has also completed an assessment on the levels of heavy metals present in the drug product by ICP-MS. Test results showed that heavy metal impurities (b) (4) are present at or below limits specified under USP <231>/<232>

Executive Summary Section

and EP monograph for Water for injection (0.1ppm). Together, the information provided in the data package support the safety of the materials used for the construction of the container closure system.

The Firm has developed a container closure integrity test (a leak test) which is capable of detecting gross leaks. Package integrity is tested during the release of each batch. The product is tested for sterility at the time of batch release and also during stability.

(b) (4)



The stability results for these batches meet the stability acceptance criteria. The stability data from 6 month accelerated storage stability study (40°C/75% RH) and 12 month real-time storage condition (ambient, 25°C/60% RH) did not show any significant change. Based on ICH Q1E guidelines (Appendix A, guidelines for extrapolation of stability data), a shelf-life of 24 months is recommended for the proposed product. The Applicant has provided post-approval stability protocol and committed to place first three production batches on post-approval real-time stability and thereafter, to place a minimum of one production batch on the long-term stability program.

The NDA states that the proposed product will be stored at room temperature (b) (4). The proposed study does not include intermediate storage conditions (b) (4). We recommend that the firm should label the product for storage under USP controlled room temperature (20° to 25° C (68° to 77°F)).

The Applicant has claimed categorical exemption for Environmental assessment under 21CFR 25.31 (b) and (c), which is acceptable.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

Chemist Name/Date: Same date as draft review
Chemistry Branch Chief/ Name/Date
Project Manager Name/Date

C. CC Block

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/s/

MUTHUKUMAR RAMASWAMY
06/30/2011

ALI H AL HAKIM
07/01/2011

Memo to: NDA 22305

Subject: CMC Discipline Letter for NDA 22305

From: Muthukumar Ramaswamy and Ali Al-Hakim

Through: Andrea Leonard-Segal, M.D., M.S. Director, Division of Nonprescription Clinical Evaluation and Phong Do.

Date: April 10, 2011

The Applicant has proposed to package the drug product in 16 and 32 oz immediate containers (bottles) without an eye cup or nozzle. The proposed packaging for 16 and 32 oz bottle is not acceptable and does not conform to drug product labeling directions as outlined in 21 CFR § 349.78(d).

We request that a CMC Discipline Letter be issued for the following:

- (1) The Applicant needs to include either the eye cup or the nozzle for packaging the product in 16 and 32 oz bottles and provide appropriate sterility testing and supportive stability data for the same.
- (2) The copies of (b) (4) and conductivity data (for purified water) provided in the NDA Filing Communication Response are not legible. The Applicant should submit the (b) (4) and conductivity data for purified water batches manufactured since 2007 to date in a tabular format for Agency review.
- (3) The Applicant should provide samples of the proposed drug product representing each of the commercial packaging configurations.

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

/s/

MUTHUKUMAR RAMASWAMY
04/12/2011

ALI H AL HAKIM
04/12/2011

NDA 22-305

Eye Wash

Niagara Pharmaceuticals

Muthukumar Ramaswamy, Ph.D.

Division of Non-Prescription Products and Clinical Evaluation (DNCE)

Table of Contents

Chemistry Review Data Sheet.....3

The Executive Summary6

I. Recommendations6

 A. Recommendation and Conclusion on Approvability:..... 6

 B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable : none 6

II. Summary of Chemistry Assessments6

 A. Description of the Drug Product(s) and Drug Substance(s) 6

 B. Description of How the Drug Product is Intended to be Used..... 6

 C. Basis for Approvability or Not-Approval Recommendation 7

III. Administrative.....8

 A. Reviewer’s Signature..... 8

 B. Endorsement Block..... 9

 C. CC Block 9

Chemistry Assessment10

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data..... 10

 S DRUG SUBSTANCE..... 10

 P DRUG PRODUCT 14

 A APPENDICES 42

 R REGIONAL INFORMATION 42

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 142

 A. Labeling & Package Insert: 42

 Environmental Assessment Or Claim Of Categorical Exclusion: 44

Executive Summary Section

Chemistry Review Data Sheet

1. NDA 22305

2. REVIEW #: 1

3. REVIEW DATE: 03-15-11

4. REVIEWER: Muthukumar Ramaswamy, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Initial Quality Assessment (CMC) in DARRTS	4/17/2008
Refuse to file letter in DARRTS	4/25/2008
Initial Quality Assessment (CMC) in DARRTS	12/10/2010
Filing Communication (Filing issues Identified) in DARRTS	1/07/2011
PIND Meeting correspondence	09/6/2007

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original application	11/01/10

7. NAME & ADDRESS OF APPLICANT:

Name:	Niagara Pharmaceuticals, Inc
Address:	60 INNOVATION DR , FLAMBOROUGH, ONTARIO, CA L9H 7P3
Representative:	R. Schiff
Telephone:	973-227-1830

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: Eye Wash

Non-Proprietary Name (USAN): Purified water Code Name/# (ONDC only):

1. Chem. Type/Submission Priority (ONDC only):

- Chem. Type: Type 3
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: To Flush eyes of foreign objects

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 98.3%

13. ROUTE OF ADMINISTRATION: Topical

Executive Summary Section

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: Purified Water

Molecular weight: 18

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	2/22/11	LOA Letter dated august 21, 2009
	III		1	Adequate	5/24/2008	LOA Letter dated 0Aug.18, 2009. Reviewed by R. Agarwal dated 5/24/2008.	
	III		4	N/A	2/22/11	LOA Letter dated July 7, 2008.	
	III		1,4	Adequate	09/18/2000	LOA Letter dated Aug. 19, 2009. The last review of this DMF for (b) (4) (review #8 M. J. Sloan 18-sep-2000) was found adequate.	
	III		1,4	Adequate	7/16/2004	LOA Letter dated May 4, 2010. (b) (4) Reviewed by Li Shan Hsieh on 7/16/2004. The (b) (4) meets the regulation in 21CFR.176.170(c)	
	III		1,4	Adequate	09/07/10	DMF was reviewed by A. Banerjee on 09/07/10	

¹ Action codes for DMF Table: <http://darrts.fda.gov:7777/darrts/ViewDocument?documentId=090140af801b3f2c>

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:

Executive Summary Section

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Adequate	1/18/11	Not Applicable
Pharm./Tox.	Review pending	TBD	Wafa Harrouk
LNC	N/A		
EA	NA		
Microbiology	Review pending	NA	Denise Miller

Executive Summary Section

The Chemistry Review for NDA 22305

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability:

From CMC perspective, the NDA application is not recommended for approval. Microbiology review, biopharm waiver, and chemistry issues are pending (process validation package is inadequate, and a minimum of 12 months of stability data are needed to support the requested expiry dating).

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)

The proposed eye wash product is a sterile aqueous solution. The eye wash contains (b) (4) boric acid, (b) (4) sodium borate (b) (4) sodium chloride (b) (4) and purified water as active ingredient. The eye wash solution is packaged in 1, 4, 8, 16 and 32 oz size HDPE container with appropriate type (b) (4) closure and tamper evident seal. The 1 and 4 oz bottles are provided with (b) (4) natural dropper tip and extended tip cap. Both 8 oz and 16 oz bottles are provided with a natural plug containing an orifice and a white cap. The 16 and 32 bottles are provided with (b) (4) cap (closure with sealing gasket). The proposed product is for single-use only. The packaged product is (b) (4). Eye cup for use with 16 oz and 32 oz bottles is not provided as part of the commercial packaging.

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

The eye wash solution is proposed for cleansing the eye to help relieve irritation, (b) (4) burning, (b) (4) by removing loose foreign material, (b) (4). The proposed product is for single-use only. Flushing the affected eye as needed and controlling the rate of flow of solution by pressure on the bottle. Eye cups are required when using eye wash solution packaged in 16 and 32 oz bottles. The NDA states that distributor will repackage the product with an eye cup. **The label for 16 and 32 oz bottle does not specify the use of eye wash solution with an eye cup and is not in conformance with CFR 349.78.**

The labeling section contains the following warnings and the label conforms to CFR 349.50 and 359.78 sections:

- a) Applicable to 1-8 oz bottles: To avoid contamination, do not touch tip of container to any surface. Do not reuse. Once opened, discard (ref. CFR 349.50).

Applicable to all size products:

- b) Consult a doctor, if you experience eye pain, changes in vision, continued redness or irritation of the eye, or if the condition worsens or persists.
- c) "Obtain immediate medical treatment for all open wounds in or near the eyes."
- d) "If solutions changes color or become cloudy do not use."
- e) Do not use on broken skin
- f) Stop using eye wash and ask a doctor if you experience an open wound near the eyes.

Executive Summary Section

The manufacture's label also contains an additional warning that the consumer should not use the product if the tamper evident seal is missing or broken.

C. Basis for Approvability or Not-Approval Recommendation

The NDA is not approvable as chemistry issues are not resolved and completion of microbiology review for sterilization process validation is pending.

The NDA contains CMC information for a single-use only sterile eye wash solution packaged in 1-32 oz HDPE bottles. The containers are provided with appropriate type closure and tamper evident seal. The eye wash solution contains (b) (4) boric acid and (b) (4) sodium borate (b) (4) sodium chloride (b) (4), and purified water as active ingredient. The proposed drug product meets the definition of eye wash product proposed under CFR 349.20.

The inactive ingredients in the drug product are compendial grade excipients and the proposed specification for these ingredients meet USP/NF monograph specifications. The active ingredient (purified water) is manufactured using a qualified water purification system and is produced on-demand to meet the drug product manufacturing needs. The proposed specification for the active ingredient includes (b) (4), conductivity, and total aerobic count and absence of coli forms, which meet USP monograph requirements. Stability data is not needed for the purified water is not provided as the water purification system generates purified water on demand to meet the manufacturing needs.

The NDA contains adequate information on the composition, method of manufacture, in-process controls, test methods, and specification for the proposed drug product. The manufacturing process for the drug product involves dissolution of boric acid, sodium borate, and sodium chloride salts in purified water (active ingredient) filled in a stainless steel tank. After dissolution, the bulk eye wash solution is filled in 1-32 oz size HDPE containers and capped with appropriate type polypropylene closures and tamper evident PVC seals in a packaging line.

(b) (4)

(b) (4)

The NDA contains adequate in-process controls for bulk eye wash manufacturing, filling and packaging operations. The proposed final specification for the product meets the USP monograph specification for eye wash solution. The finished product is tested for various physical and chemical attributes (appearance, color, assay of sodium chloride and boric acid, osmolality, specific gravity, particulate matter); microbiological attributes (sterility) and packaging integrity. The NDA contains acceptable method validation for the assay used for the determination of borate and chloride content.

The NDA contains information on the batch record used to manufacture the stability batches,. The batch record provides a description of the equipment and process used for the manufacture the drug product.

This NDA is a resubmission of the original new drug application that contained CMC information for an eye wash formulation (b) (4). The Applicant has submitted the process validation package completed for the original

Executive Summary Section

product to support the reformulated eye wash product. *The Applicant should provide process validation data to support the manufacturing of the proposed preservative free eye wash product.*

The NDA contains batch results for 3 batches of eye wash solution and the test results for these batches met the proposed release specification for the product. The Firm uses USP certified reference standards (b) (4) for testing Purified Water.

The NDA contains information on specification, material of construction, and engineering drawings for packaging components. The Applicant also provided appropriate reference to the DMFs associated with the packaging components. *The Firm uses 1-32 oz containers from high density polyethylene resin (HDPE resin) and (b) (4) closures for packaging the eye wash product, which meet regulations for food contact materials (21 CFR 177.1520).* The Firm provided data to support that the proposed container meet USP <661>/<671> test requirements.

The Applicant also provided adequate method validation information for the method (GC/MS method) used for detecting leachables present in the eye wash product. The Firm has completed an leachable study, which indicated that (b) (4) eye wash solutions contain known below detection limit and unknown leachables at <1 ppm level. *The container closure system data package does not contain any USP Biological Reactivity Test data to support the safety of the material used to construct the proposed container closure system.*

The Firm has developed container closure integrity test (a leak test) which is capable of detecting gross leaks. Package integrity is tested during the release of each batch. The adequacy of the proposed container closure integrity test for assuring the sterility of the eye wash product will be assessed by the microbiology reviewer.

(b) (4)

Stability results for these batches met the stability acceptance criteria. The proposed stability protocol does not include an evaluation of stability under intermediate storage condition. An information request has been sent to the Applicant to provide a minimum of 6 months of accelerated stability and 12 months of real-time stability data for the proposed product

The Applicant has provided post-approval stability protocol and committed to place first three production batches on post-approval real-time stability and thereafter, to place a minimum of one production batch on the long-term stability program.

The NDA states that the proposed product will be stored at room temperature (b) (4). The proposed study does not include intermediate storage conditions (b) (4). Therefore the firm label the product for storage under USP controlled room temperature (20° to 25° C (68° to 77°F)).

The Applicant has claimed categorical exemption for Environmental assessment under 21CFR 25.31 (b) and (c), which is acceptable. The Applicant has also filed a biopharm waiver for not conducting bioequivalence studies for the proposed eye wash product. The request will be evaluated by biopharm reviewer.

III. Administrative

A. Reviewer's Signature

Executive Summary Section

B. Endorsement Block

Chemist Name/Date: Same date as draft review
Chemistry Team Leader Name/Date
Project Manager Name/Date

C. CC Block

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/s/

MUTHUKUMAR RAMASWAMY
02/23/2011

ALI H AL HAKIM
02/23/2011

ONDQA Initial Quality Assessment for NDA Resubmission
Muthukumar Ramaswamy, Ph.D., Division of Pre-marketing Assessment III, Branch VII

NDA: 22305

Applicant: Niagara Pharmaceuticals, Inc.

Stamp Date: Nov.1, 2010

PDUFA Date: September 1, 2011

Proposed Proprietary Name: Eye Wash

Established Name: Purified water,

Dosage form and strength: Solution or Irrigant/ NA

CMC-Lead: Swapn De, Ph.D. ONDQA

ONDQA Fileability Recommendation: Yes

Primary reviewer: Muthukumar Ramaswamy, Ph.D.

Time goals:

Filing Decision: Dec. 31, 2010

Filing review issues "Day 74": Jan. 13, 2011

Wrap-Up meeting: Jun. 13, 2011

Reviews due: Jul. 01, 2011

PDUFA date: Sep. 01, 2011

Relevant DMFs:

DMF #  (b) (4)
DMF #
DMF #
DMF #
DMF #
DMF #
DMF #

CONSULTS/ CMC RELATED

REVIEWS

COMMENT

Biopharmaceutics

NA

CDRH or CBER

Not Applicable

EA

NA.

EES

EER was created

OSE

Labeling consult request will be sent as part of DMEP's request.

Methods Validation

Not applicable

Microbiology

Endotoxin, bioburden, sterility, and  (b) (4)

Pharm/Tox

Risk assessment on leachables may be requested

Labeling and Nomenclature

OSE/DMEPA

A. Summary

Niagara Pharmaceuticals has resubmitted a 505(b) (2) New Drug Application (NDA) for the marketing of Eyewash (purified water (b) (4)) solution proposed for the flushing of foreign objects in eye. The original submission was filed on January 30, 2008 (b) (4). The Agency refused to file the submission due to insufficient information to complete a substantial review.

The Firm resubmitted the NDA application on Oct. 28, 2010. The proposed drug product is a sterile, isotonic, pH-adjusted, *preservative free* buffered aqueous solution packaged in single-use HDPE plastic bottles (1oz to 32oz) equipped with (b) (4) e caps or dropper tip caps. The eye wash solution contains 98.3% of purified water, USP, (b) (4) boric acid, NF; (b) (4) sodium borate, NF; and (b) (4) sodium chloride, USP. The NDA states that the proposed ingredients meet compendial requirements.

With the exception of the (b) (4) the proposed product meets the OTC monograph requirements as specified in 21 CFR 349.20 for eyewashes. To meet the sterility requirement, the product is (b) (4).

The Application contains manufacturer's name, address and contact information. The NDA describes the specification and manufacturing information, performance qualification information for the active ingredient purified water and it meets the USP monograph requirements.

The NDA describes the components and composition of the drug product, batch formula, process description, and process control used to control the quality of the product. The manufacturing and filling operations are carried out in (b) (4)

The NDA contains specifications (test methods and acceptance criteria) for controlling the quality of active ingredient, raw materials, packaging components, and finished product.

The Application does not contain any endotoxin limit for the finished product as well as raw materials and packaging components used in the manufacturing of finished product.

It contains method validation information for the analytical methods (assay of borate and chloride by ion chromatography and leachables by GC/MS). The Applicant has completed a study to demonstrate the effect of (b) (4) on the quality of the finished product using (b) (4) product packaged in plastic and glass container. The study evaluated the change in the borate and chloride content (b) (4). The study also evaluated the levels of leachables present in the finished product stored in (b) (4) container.

The application contains information all packaging components associated with the finished product and the Applicant has provided reference to DMF # associated with the packaging components.

The NDA submission contains 3 months. of accelerated and real-time stability data for the lowest and highest fill volume product. An expiration date of (b) (4) is proposed for the product and is

ONDQA Initial Quality Assessment for NDA Resubmission
Muthukumar Ramaswamy, Ph.D., Division of Pre-marketing Assessment III, Branch VII

not supported by the data provided in the submission. A minimum of 12 mo real-time stability data along with 6 month data under accelerated conditions is needed to support the NDA.

B. Comments/Recommendation:

The application is fileable from CMC and quality perspective.

1. Provide process validation (bulk solution manufacturing, filling and sterilization) data for the proposed preservative free product or justify your approach.
2. Provide endotoxin limit for the finished product as well as raw materials and packaging components used in the manufacturing of finished product.
3. Provide 12 months of real-time stability data along with 6 month stability data under accelerated conditions to support the stability of your proposed eye was product.

CHEMISTRY NDA FILEABILITY CHECKLIST

Is the CMC Section of Application Fileable? Yes

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:

	Content Parameter	Yes	No	Comment
1	Is the section legible, organized, indexed, and paginated adequately?	x		
2	Are ALL of the manufacturing and testing sites (including contract sites) identified with full street addresses (and CFNs, if applicable)?	x		CFN missing for some sites
3	Is a statement provided to indicate whether each manufacturing or testing site is ready for inspection or, if not, when it will be ready?	x		
4	Is a statement on the Environmental Impact provided as required in 21 CFR 314.50(d)(1)(iii)?	X		
5	Is information on the Drug Substance provided as required in 21 CFR 314.50(d)(1)(i)?	x		
6	Is information on the Drug Product provided as required in 21 CFR 314.50(d)(1)(ii)?	x		
7	If applicable, has all information requested during the IND phases and at the pre-NDA meetings been included?			Not applicable. Resubmission
8	Have draft container labels and package insert been provided?	X		Label in the SPL format provided
9	Have all DMF References been identified?	X		
10	Is information on the investigational formulations included?		X	Not applicable eye wash product
11	Is information on the methods validation included?	x		
12	If applicable, is documentation on the sterilization process validation included?	X		

Comments to the Applicant

1. Provide process validation (bulk solution manufacturing, filling and sterilization) data for the proposed preservative free product or justify your approach.
2. Provide endotoxin limit for the finished product as well as raw materials and packaging components used in the manufacturing of finished product.
3. Provide 12 months of real-time stability data along with 6 month stability data under accelerated conditions to support the stability of your proposed eye was product

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/s/

MUTHUKUMAR RAMASWAMY
12/10/2010

ALI H AL HAKIM
12/10/2010

Initial Quality Assessment
Branch III
Pre-Marketing Assessment Division II

OND Division: Division of Nonprescription Clinical Evaluation
NDA: 22-305
Applicant: Niagara Pharmaceuticals, Inc.
Stamp Date: Feb. 26, 2008
PDUFA Date: Dec. 26, 2008
Trademark: Eyewash
Established Name: Purified Water
Dosage Form: Irrigation
Route of Administration: Topical
Indication: Flush eyes of foreign objects

PAL: Shulin Ding

	YES	NO
ONDQA Fileability:	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Comments for 74-Day Letter	<input checked="" type="checkbox"/>	<input type="checkbox"/>

Summary and Critical Issues:

A. Summary

Niagara Pharmaceuticals is submitting a 505(b) (2) New Drug Application (NDA) for the nonprescription marketing of Eyewash (purified water (b) (4)) irrigation for the indication of flushing eyes of foreign objects. The product meets the OTC monograph requirements in 21 CFR 349.20 for eyewashes but is treated as a new drug due to its (b) (4). According to 21 CFR 310.502 (a) (11), all drugs that are sterilized by (b) (4) require a New Drug Application.

(b) (4)



temperature and humidity.” The batch size(s) of these stability batches and their container/closure systems are uncertain. The largest proposed commercial batch size is (b) (4)

B. Critical issues for review

Drug Product Established Name

- According to USP and ONDQA internal established practice, the dosage form (b) (4) However, the proposed product is also OTC monographed under Eyewashes. There may be a desire to keep “eye wash” as the established name for this product so that it would be consistent with other similar eye wash products on the OTC market.

(b)
)
(4)
)

Drug Product Specification

- The following important product attributes are missing: minimal fill, water loss, packaging integrity, and osmolality. The applicant was advised by the FDA in the pre-IND meeting to include osmolality in the drug product specification.

Drug Product Container/Closure Systems

- There is no description for to-be-marketed packaging configurations.
- Most of packaging components are not referenced to a DMF. There is a general lack of information in the NDA for resins and colorants.
- Test results of USP<661> are not provided for immediate packaging components. USP<661> describes the standards for the materials of which pharmaceutical containers principally are made.
- No information is provided for label components such as inks, adhesive, and varnish.
- Temper-resistant package which is required for an OTC product (21 CFR 211.132) is not included in the packaging system.
- Some packaging components proposed are not in compliance with OTC Eyewash monograph 21 CFR 349.78(d) where an eyecup or a nozzle applicator is required.

Drug Product stability

- The relevance of the provided stability data to commercial batches needs to be critically reviewed because the batch size(s) of stability batches and their container/closure systems are uncertain.
- The stability data package is highly deficient. Noted issues include (1) only two fill sizes (b) (4) are studied, (2) only one time point (36 months) is provided, and (3) important tests such as particulate matter, water loss, and packaging integrity are missing. The 36 month stability samples actually failed

to meet the physical appearance specification (slightly yellowish when it is supposedly to be colorless according to the specification).

- [REDACTED] (b) (4)

Extractables

- The extractables study conducted by the applicant to support this NDA is inadequate because HPLC was not used in the investigation, and there is no monitoring in stability samples. It is unclear whether label components such as inks, adhesive and varnish were included in the study. The inclusion of label components is especially important for the [REDACTED] (b) (4). It is also necessary to compare extractables profile between [REDACTED] (b) (4) products.

Drug Product Impurity Characterization

- Impurities are not adequately characterized because (1) no information is provided regarding the degradants produced [REDACTED] (b) (4).

The evaluation of impurities is critical because a clinical safety study will be needed if there are significantly different impurities between [REDACTED] (b) (4) product and [REDACTED] (b) (4) product (PIND meeting minutes).

C. Comments for 74-Day Letter:

The NDA is refused to be filed for administrative, clinical and non-clinical issues. Since there are serious CMC review issues with this NDA, the following are additional comments to be conveyed to the applicant in the RTF letter:

1. A comprehensive study on impurities/degradants is strongly recommended for the resubmission of the NDA. The characterization work should employ analytical technologies such as HPLC, GC, and Mass. Please refer to ICH guideline Q3B(R) for reporting/identification/qualification thresholds. The study must include a comprehensive comparison of impurity profile [REDACTED] (b) (4), and monitoring of impurity profile throughout the registration stability studies using stability-indicating methods.
2. A comprehensive study on extractables is strongly recommended. The study must employ HPLC/Mass in addition to GC/Mass as the analytic methods. The study must be conducted in the samples packaged in the to-be-marketed container/closure systems [REDACTED] (b) (4) in the same manner as that for the commercial batches. Pertinent label components (such as inks, adhesives, and varnishes) and appropriate

controls such as glass bottle must be included in the study. A comparison of extractables profile [REDACTED] (b) (4) product must be performed. Extractables above 10 ppm needs be identified. Extractables above 20 ppm needs to be qualified.

3. The following tests with appropriate acceptance criteria should be added to drug product specification: particulate matter, minimal fill (release only), water loss, packaging integrity, and osmolality.
4. The registration stability studies should comply with ICH Q1A. In addition to those tests included in the drug product specification, you should also monitor extractables in the stability studies throughout the study period with a glass control. A check in antimicrobial effectiveness test (USP<51>) should also be included in the stability protocol. If you don't plan to conduct stability studies for each packaging configuration, please refer to ICH guideline Q1D for proper bracketing strategy, and provide a strong scientific justification in the NDA resubmission.
5. The certificates of analysis and stability data tables should contain the numerical test results or actual reading. A record of "pass", "conform" or "fail" is unacceptable. We recommend you to use color standards such as those from European Pharmacopeia to evaluate the color of the proposed product.
6. A clear description must be provided for each to-be-marketed packaging configuration, and it must include information for each packaging component including ink/adhesive/varnish.
7. Chemistry, manufacturing and controls information for each packaging component should be provided in the NDA or referenced to a DMF. Please refer to CDER Guidance for Industry "Container Closure Systems for Packaging Human Drugs and Biologics" for information which should be submitted in a NDA. The proposed packaging components must comply with USP<661>.
8. Please be advised that a temper-resistant package is required for an OTC product (21 CFR 211.132), and that an eyecup or a nozzle applicator is required for an OTC monographed eyewash product (21 CFR 349.78(d)).

D. Comments/Recommendation:

The application is fileable from CMC and quality perspective. The NDA is refused to be filed because of filing issues with other disciplines.

The major CMC review issues with this NDA include drug product specification, stability, extractables, container/closure system, and comparative impurity profile [REDACTED] (b) (4)

Shulin Ding
Pharmaceutical Assessment Lead

Moo Jhong Rhee
Chief, Branch III

Filing Checklists

A. Administrative Checklists

YES	NO		Comments
x		On its face, is the section organized adequately?	
x		Is the section indexed and paginated adequately?	
x		On its face, is the section legible?	
x		Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	
x		Has an environmental assessment report or categorical exclusion been provided?	

B. Technical Checklists

1. Drug Substance: Purified Water, USP

x		Does the section contain synthetic scheme with in-process parameters?	
	x	Does the section contain structural elucidation data?	Not applicable
x		Does the section contain specifications?	USP
	x	Does the section contain information on impurities?	Compendial material
	x	Does the section contain validation data for analytical methods?	Compendial method
	x	Does the section contain container and closure information?	Not applicable
	x	Does the section contain stability data?	Not applicable

2. Drug Product

x		Does the section contain manufacturing process with in-process controls?	
x		Does the section contain quality controls of excipients?	
x		Does the section contain information on composition?	
x		Does the section contain specifications?	
x		Does the section contain information on degradation products?	Inadequate.
x		Does the section contain validation data for analytical methods?	
x		Does the section contain information on container and closure systems?	
x		Does the section contain stability data with a proposed expiration date?	
x		Does the section contain information on labels of container and cartons?	
x		Does the section contain tradename and established name?	Dosage form not proposed.

C. Review Issues

x		Has all information requested during the IND phases, and at the pre-NDA meetings been included?	Osmolality is not included in the drug product specification.
	x	Is a team review recommended?	
x		Are DMFs adequately referenced?	

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this page is the manifestation of the electronic signature.**

/s/

Shulin Ding
4/17/2008 11:28:21 AM
CHEMIST

Moo-Jhong Rhee
4/17/2008 12:59:17 PM
CHEMIST
Chief, Branch III