CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022305Orig1s000

MEDICAL REVIEW(S)

Medical Officer's Review of NDA 22-305
Review #2

NDA 22-305	Submission :	May 31, 2011
	Reviewer Received:	June 1, 2011
	Review Date:	June 22, 2011

Sponsor:

Niagara Pharmaceuticals, Inc
60 Innovation Drive
Flamborough, Ontario L9H 7P3
Canada

Drug:

Purified Water, 98.3%

Submitted:

The applicant has submitted revised carton and container labels in response to the Agency's labeling comments letter dated May 12, 2011.

Reviewer's Comments: The word (b) (4) is recommended for removal from the drugs established name on each of the carton and container labels. The phrase "If swallowed, get medical help or contact a Poison Control Center right away" is not appropriate because swallowing the solution is not harmful.

Recommendations:

1. The word (b) (4) is recommended for removal from the drugs established name on each of the carton and container labels.

2. The phrase “If swallowed, get medical help or contact a Poison Control Center right away” is not appropriate because swallowing the solution is not harmful.

Jennifer D. Harris, MD
Medical Officer

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

JENNIFER D HARRIS
07/20/2011

WILLIAM M BOYD
07/20/2011

CLINICAL REVIEW

Application Type	505(b)(2)
Application Number(s)	NDA 22-305
Priority or Standard	Standard
Submit Date(s)	October 28, 2010
Received Date(s)	November 1, 2010
PDUFA Goal Date	September 1, 2011
Division / Office	DNCE ODE IV
Reviewer Name(s)	Victor Alexander, MD, MSPH
Review Completion Date	June 22, 2011
Established Name	Purified water 98.3%
(Proposed) Trade Name	Pur-Wash
Therapeutic Class	Miscellaneous ophthalmics
Applicant	Niagara Pharmaceuticals, Inc.
Formulation(s)	Ophthalmic solution
Dosing Regimen	Flush affected eye as needed, controlling solution rate of flow
Indication(s)	For cleansing the eye to help relieve irritation, (b) (4) burning, (b) (4) by removing loose foreign material, (b) (4)
Intended Population(s)	General consumer use

Table of Contents

Table of Tables

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical perspective, this reviewer recommends that NDA 22-305 Pur-Wash Eyewash (Purified Water 98.3%) Sterile Solution be approved for cleansing the eye to help relieve irritation, (b) (4) burning, (b) (4) by removing loose foreign material, (b) (4)

All proposed container sizes, closures, and labeling are acceptable and should be approved. The sponsor seeks approval for five container sizes of its product: 1 oz (30 mL), 4 oz (118 mL), 8 oz (236 mL), 16 oz (473 mL), and 32 oz (946 mL). Each container is equipped with either a nozzle equivalent closure or a sterile eyecup which can be affixed to the container opening.

The revised labeling submitted is acceptable, with modest changes. This reviewer recommends that:

- the sponsor delete the term "(b) (4)" from the revised product statement "Sterile (b) (4) Solution" placed on the PDP.
- the tamper evident seal should be overprinted in English only.

1.2 Risk Benefit Assessment

The risk benefit of eyewash products under the Ophthalmic Products for Over-the-Counter Human User final monograph (21 CFR §349) is well established.

Provided the final CMC review shows there are no meaningful changes to the components after (b) (4), no clinical studies are needed to support approval of this product. The microbiology reviewer needs to conclude that (b) (4) of this product formulation without a preservative is effective to ensure and maintain sterility during the product's requested shelf life.

Review of the sponsor's postmarketing data for a similar eyewash product marketed in Canada, review of limited data from FDA's AERS database, and a search for published reports of clinical toxicity from exposure to topical ophthalmic solutions containing purified water, failed to identify any new safety signals or clinical concerns for this product when used as directed.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no postmarketing recommendations for this product.

1.4 Recommendations for Postmarket Requirements and Commitments

I have no postmarketing recommendations for this product beyond routine pharmacovigilance.

2 Introduction and Regulatory Background

The sponsor seeks approval for an OTC single use, sterile eyewash product for general consumer use to flush the eyes of loose debris, [redacted]. This eyewash product contains 98.3% purified water as the active ingredient, and the drug product is sterilized by [redacted]. The sponsor previously submitted NDA 22-305 for an earlier version of this product, [redacted] on January 30, 2008.

FDA determined the original application was not sufficiently complete to permit a substantive review under 21 CFR 314.101(d), and informed the sponsor it had been given a "refuse to file" status in a letter dated April 25, 2008. This letter contained 10 items listed under "refuse to file", and 15 other comments including a number of CMC related matters, the lack of non-clinical information provided, absence of characterization of leachables and new impurities/degradants, and administrative deficiencies. See section 2.5 below for further details.

The sponsor submitted two CMC study protocols under PIND 77,883 and received FDA advice on November 5, 2008. The sponsor subsequently elected to reformulate the product by [redacted] as FDA had advised.

The sponsor has provided new CMC and microbiological study data, changed the product name, and revised the labeling in this new submission dated November 1, 2010.

The sponsor proposes to rely on the Ophthalmic Products for Over-the-Counter Human Use final monograph (21 CFR §349). Eyewash is listed in the monograph in 21 CFR §349 - Ophthalmic Drug Products for Over-The- Counter Human Use, Subpart B Active Ingredients, Sec. 349.20 Eyewashes. Drug products which meet these regulatory requirements are recognized as safe and effective and can be marketed as OTC if there are no deviations from the established monograph. The risk/benefit of eyewash products has been established for products that follow the OTC monograph.

The current product is sterilized by [redacted]. Under 21 CFR §310.[redacted], all drug products sterilized by [redacted] require an NDA.

This product deviates from the OTC monograph for eyewash products since it does not contain antimicrobial preservatives. However, this NDA does not require new nonclinical or clinical testing provided the [redacted] does not change the chemistry specifications when comparing the [redacted] products. Further, the sponsor argues that a preservative agent should not be required since the product is exclusively intended for a single use where the entire container volume is to be consumed or discarded once the product is opened.

2.1 Product Information

The sponsor seeks approval for an OTC single use, sterile eyewash product for general consumer use to flush the eyes of loose debris, (b) (4)

Table 1: Eyewash Product Ingredients

Ingredient name	Active/Inactive	CAS#	%
Purified Water	Active	N/A	98.3
Boric Acid	Inactive	10043-35-3	(b) (4)
Sodium Borate	Inactive	1330-43-4	
Sodium Chloride	Inactive	7647-14-5	

Source: Adapted from Sponsor's Information Response email to FDA, 11/17/2010

This eyewash solution contains purified water USP (98.3%), boric acid N.F./USP (b) (4), sodium chloride USP (b) (4) and sodium borate N.F. (b) (4). All ingredients meet USP or NF specifications. The inactive ingredients in the drug product are compendial grade excipients. The active ingredient is purified water; the boric acid and sodium borate (b) (4), and the sodium chloride (b) (4). The final drug product is sterilized by (b) (4), which is the primary reason this product requires review under an NDA (see 21 CFR §310.(b) (4).

The sponsor seeks approval for five container sizes of its product: 1 oz (30 mL), 4 oz (118 mL), 8 oz (236 mL), 16 oz (473 mL), and 32 oz (946 mL). Each container is equipped with a nozzle equivalent closure: a natural dropper tip and extended tip cap (1 oz, 4 oz) or a natural plug containing an orifice and a cap (8 oz, 16 oz sizes); or else a sterile eyecup which can be affixed to the container opening (16 oz, 32 oz sizes) in the same package. Only the 16 oz size comes with a choice of either a nozzle closure or a sterile eyecup. Both container closure methods are designed to permit controlled flow of eyewash product by means of variable pressure while holding the container and flushing the affected eye(s).

2.2 Tables of Currently Available Treatments for Proposed Indications

There are no approved NDAs for this OTC indication. There are a number of eyewash products marketed under the OTC monograph.

FDA evaluated the size of OTC eyewash market in 2003, as described in the economic impact section of the Ophthalmic Drug Products for Over-the-Counter Human Use; Final Monograph; Technical Amendment.[1] The agency believed 25 manufacturers produced approximately 40 eyewash products, which were represented by up to (b) (4) stock keeping units (SKUs). The agency reviewed information on the manufacturers of OTC eyewash drug products (North American Industry Classification System Code 325412: Pharmaceutical Preparations), and believed 22 of

[1] 68 Federal Register 7919, Wednesday, February 19, 2003

the 25 manufacturers were small entities. These small entities had average annual revenues of (b) (4). The two smallest of these small entities had reported annual revenues of approximately (b) (4).

2.3 Availability of Proposed Active Ingredient in the United States

Purified water is used as the active ingredient in eyewash products marketed under the OTC final monograph, and is widely used as an inactive ingredient in numerous drug products. The only NDA's for sterile water in the FDA Orange Book are for injection or irrigation.

2.4 Important Safety Issues With Consideration to Related Drugs

Purified water is generally recognized as safe and effective for this use under the monograph. There are no known significant safety issues.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The sponsor filed a presubmission PIND 77,883 for their product named (b) (4) Eye Wash on June 29, 2007. FDA held a Type B teleconference meeting with the sponsor on September 6, 2007 to discuss the submission of an NDA.

The following items were addressed during this teleconference:

- The proposed Quality information content including a demonstration of sterility by (b) (4) as well as non-interference or no meaningful changes to the components of the eyewash, and the validation of sterilization would be acceptable to the Agency.
- FDA stated a chemical comparison is required between the (b) (4) product and the (b) (4) product. If there are significantly different impurities, a clinical safety study to support the formulation will be needed. If review of the data shows no difference in chemistry, then reference can be made to the monograph to support the NDA.
- The Sponsor stated that the stability testing for the (b) (4) sterilized product will be at periodic time points and would show no differences in the product. The Agency agreed to the periodic time points for stability testing.
- FDA recommended a one time extractable/leachable study be performed on the (b) (4) sterilized drug product with appropriate control sample using appropriate screening techniques to detect extractables/leachables.
- FDA recommended the following tests be added to the finished product specifications: osmolality (b) (4)
- FDA noted the proposed product would require a New Drug Application (NDA) because the product will be (b) (4). If the manufacturing procedures change, and the product is no longer sterilized by (b) (4), yet otherwise meets the requirements described in 21 CFR §349, an NDA may not be required.

As described above in the section 2 Introduction, FDA refused to file NDA 22-305 on April 25, 2008 and provided the sponsor with detailed comments.

FDA refused to file this application under 21 CFR §314.101(d) for the following reasons:

1. The field copy required by 21 CFR §314.50 was not submitted.
2. The application form (Form 356h) was signed only by the foreign applicant. The U.S. agent did not sign the 356h as required by 21 CFR §314.50(a)(5).
3. The index did not include reference to Modules 4 & 5 as required by 21 CFR §314.50(b).
4. The summary required by 21 CFR §314.50(c) was not submitted.
5. The field copy certification required by 21 CFR §314.50(d)(1)(v) was not submitted.
6. The non-clinical pharmacology and toxicology section required by 21 CFR §314.50(d)(2) contained no information except a statement that the proposed product was a monographed drug and that the monograph requirements had been met. The eyewash monograph active ingredients at 21 CFR §349.20 referenced in the cover letter could not be referenced to support this NDA for non-clinical pharmacology and toxicology purposes because the preliminary chemistry review for this NDA indicated that there were a number of differences between the proposed (b) (4) eyewash and the (b) (4) product listed in the Ophthalmic Drug Products for Over-the-Counter Human Use monograph (21 CFR §349) addressing eyewash products. It appeared that impurities and/or degradants might be present in the product that the sponsor must characterize.
7. The clinical section required by 21 CFR §314.50(d)(5) contained no information except a statement that the proposed product was a monographed drug and that the monograph requirements had been met. As discussed during the September 6, 2007 teleconference, if the chemistry and microbiology sections of the NDA had demonstrated sterility of the product and there had been no meaningful changes to the components after (b) (4), then reference to the eyewash monograph could be used to support the NDA. However, multiple deficiencies in the chemistry and microbiology sections of the NDA were found during preliminary review, and the attributes of the proposed product appeared to deviate from the Ophthalmic Drug Products for Over-the-Counter Human Use monograph (21 CFR §349) addressing eyewash products. Thus, the sponsor is required to submit clinical safety and efficacy studies to support an NDA for this product.
8. The pediatric use section required by 21 CFR §314.50(d)(7) was not submitted.
9. The patent information (including Form 3542) required by 21 CFR §314.50(h) was not submitted.
10. The patent certification did not include the wording required by 21 CFR §314.50(i)(1)(ii).

Beyond the 10 reasons listed for the "refuse to file" status, FDA also provided the sponsor with 15 other comments based on preliminary review of the application. FDA recommended that the sponsor:

11. Include a comprehensive study of impurities and degradants.
12. Include a comprehensive study of extractables.

13. Add the following tests with appropriate acceptance criteria to the drug product specification: a. particulate matter; b. minimal fill (release only); c. water loss; d. packaging integrity; and e. osmolality.
14. Ensure the registration stability studies comply with ICH Q1A.
15. Use color standards, such as those from European Pharmacopeia, to evaluate the color of the proposed product. The certificates of analysis (COAs) and stability data tables must contain numerical test results or actual readings. Simply listing "pass," "conform," or "fail" on the COAs and stability data tables is unacceptable.
16. Provide a clear description of each to-be-marketed packaging configuration, including information for each packaging component (e.g., cap, tip, dropper, space reducer, bottle, ink, adhesive, varnish).
17. Provide chemistry, manufacturing and controls information for each packaging component, or reference a Drug Master File (DMF) for each component.
18. Provide container/closure integrity validation results for all proposed container/closure configurations.
19. Provide tamper-resistant packaging as required for all OTC products (see 21 CFR §211.132).
20. Package the proposed product with an eyecup or a nozzle applicator to correspond with the directions prescribed in 21 CFR §349.78(d), if they intend to reference the eyewash monograph at 21 CFR §349.78 for part of the application.
21. Reconsider the proposed product name. If the sponsor intends to reference the Ophthalmic Drug Products for Over-the-Counter Human Use monograph (21 CFR §349) for eyewash products to support the application, the drug product cannot be called (b) (4)
22. Include annotated font specifications for the "Drug Facts" label in accordance with 21 CFR §201.66(d).
23. Include a User Fee Cover Sheet (Form 3397).
24. Include a Debarment Certification using the wording in the Federal Food, Drug, and Cosmetic Act Section 306(k)(1).
25. Must address the PREA requirements in the resubmission of this NDA The Pediatric Research Equity Act (PREA) of 2003 requires that all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and/or new dosing regimens contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. Since the NDA proposes a new dosage form, the application is subject to the PREA requirements.

Items 6, 7 and 8 in the "refuse to file" list above, and items 20, 21, and 25 in the comments list are especially relevant clinically. Each has been addressed in the NDA resubmission. The other items are CMC issues or administrative items and will be addressed in the respective discipline reviews.

The sponsor submitted two CMC study protocols under PIND 77,883 and received FDA advice on November 5, 2008. FDA recommended that the sponsor consider (b) (4) from the formulation since data provided in the original submission of NDA 22-305 suggested (b) (4)

2.6 Other Relevant Background Information

Niagara Pharmaceuticals, Inc. manufactures eyewash preparations that contain purified water as the active ingredient (b) (4) . Based on the intended use as an eyewash and a skin flush solution, these products are drugs as defined in Section 201(g) of the Food, Drug, and Cosmetic Act (FD&C Act). As eyewash solutions, these preparations may also be subject to final regulations covering OTC ophthalmic drugs found at 21 CFR §349.

According to a consumer complaint, Niagara was importing into the U.S. market an eyewash which was being sterilized by (b) (4). The firm had no inspectional history and no NDA for this drug product. Based on this information, a "For Cause" assignment to Division of Field Investigations (DFI) was requested by CDER's Division of Manufacturing and Product Quality (CDER/ DMPQ).

In September, 2006, FDA conducted an inspection of sponsor's facility and determined that these products are sterilized by (b) (4). Drugs that are sterilized by (b) (4) are included in rulemaking (21 CFR §310 (b) (4). The 2006 inspection revealed significant sterility cGMP deficiencies. On (b) (4) FDA sent the sponsor a Warning Letter (WL: (b))

On September 10, 2009, based on these same facts, FDA issued an Import Alert (Import Alert 66-73) for the sponsor's Sterile Eyewash Product titled "Detention Without Physical Examination (DWPE) Of Sterile Eyewash Solution".[4] FDA District field personnel could detain without physical examination all sterile eyewash solutions manufactured by the sponsor.

On September 7-8, 2010, FDA conducted another cGMP inspection at the sponsor's facility. As of January 18, 2011, the compliance review was complete, and the inspection result was classified as "Voluntary Action Indicated" (VAI). DMPQ has issued an overall acceptable compliance recommendation. DMPQ also reviewed a recent Health Canada report for this firm.

It should be noted that after the Warning Letter in (b) (4) the sponsor opened PIND 77,883 in June, 2007 and submitted the original NDA 22-305 in January, 2008. According to the

(b) (4)

sponsor, since the Warning Letter was issued by FDA in February, 2007, their sterile eyewash product has been marketed only in Canada and there has been no U.S. distribution.

Reviewer Comment: This sponsor received an FDA Warning Letter (2007) and an Import Alert (2009) for marketing an eyewash product (b) (4) *without an NDA. The sponsor did file a PIND for the product in June, 2007 and an NDA 6 months later, though the application was given a "refuse to file" status by FDA in April, 2008. The product was reformulated and the sponsor performed FDA recommended CMC studies. The current NDA 22-305 re-submission in November, 2010 was made about 18 months after notification of FDA's "refuse to file" decision. The sponsor's manufacturing facility is in compliance with cGMP as of January, 2011 following re-inspection by FDA in September, 2010. This reviewer believes the sponsor has been reasonably diligent since 2007 in correcting compliance deficiencies and submitting appropriate data to support an NDA.*

3 Ethics and Good Clinical Practices

No clinical studies were conducted or submitted to support this NDA, as the sponsor relies on FDA findings of efficacy and safety for the monograph. Therefore certification of compliance with good clinical practices and financial disclosures are not required. The sponsor has included the required debarment certification in Module 1.3.4.

3.1 Submission Quality and Integrity

This resubmission application concerns primarily CMC issues of product sterility and stability due to the use of (b) (4) for a product formulation otherwise compatible with the requirements of the final monograph for OTC Eyewash products. The sponsor has provided substantial product quality and manufacturing data in addition to stability and microbiological data related to the (b) (4) of the drug product.

The submission contains a very limited statement in Modules 4 (Nonclinical) and 5 (Clinical) which references FDA's prior safety and efficacy conclusions to support the eyewash product containing purified water as the active ingredient, but the sponsor's reliance on these findings is acceptable. Under provisions of 21 CFR §330.11, a sponsor filing an NDA deviation from the applicable monograph, where the product meets all conditions of the applicable monograph except for the deviation for which approval is requested, may omit all information except that pertinent to the deviation. The application also provides a brief summary of postmarketing safety data for a similar eyewash product marketed in Canada, which contains a preservative.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

In the 74-day filing letter dated January 7, 2011 FDA notified the sponsor of potential CMC review issues and requested the following information:

- "Provide process validation (bulk solution manufacturing, filling and sterilization) data for your proposed preservative free drug product.
- Provide endotoxin limits for the finished drug product.
- Specify the raw materials and packaging components used in the manufacturing of the finished drug product.
- Provide 12 months of real-time and 6-months of accelerated stability data for three batches for your proposed drug product."

CMC reviewers have subsequently issued additional information requests to which the sponsor has responded. As of this date, CMC reviewers have filed two reviews in DARRTS, but their final opinion about approvability of this re-submission is pending.

The sponsor states that the "product also contains suitable tonicity agents to establish isotonicity with tears, suitable agents for establishing pH and buffering to achieve the same pH as tears."[5] Requirements in the Ophthalmic Drug Products for Over-The- Counter Human Use final monograph found at 21 CFR §349 349.20 include the following: "The active ingredient of the product is purified water. The product also contains suitable tonicity agents to establish isotonicity with tears, suitable agents for establishing pH and buffering to achieve the same pH as tears, and a suitable preservative agent."

The Advance Notice of Proposed Rulemaking and the Tentative Final Monograph for Ophthalmic Drug Products for Over-The-Counter Human Use do not provide quantitative guidance on the expected isotonicity and pH and buffering of human tears. The following information is taken from the section titled "Ophthalmic Solutions" in the chapter on Pharmaceutical Dosage Forms in the current United States Pharmacopeia- National Formulary.[6]

Normal tears have a pH of about 7.4 and possess some buffer capacity. Ideally, an ophthalmic solution should have the same pH, as well as the same isotonicity value, as lacrimal fluid. The application of a solution to the eye stimulates the flow of tears and the rapid neutralization of any excess hydrogen or hydroxyl ions within the buffer capacity of the tears. The buffer system should be selected that is nearest to the physiological pH of 7.4 and does not cause precipitation of the drug or its rapid deterioration. In some cases pH may vary between 3.5 and 8.5.

[5] NDA 22-305 Submission, Module 2.3.P.2 , p. 19, November 1, 2010.
[6] General Chapters <1151> Pharmaceutical Dosage Forms. *United States Pharmacopeia and National Formulary* (USP 34-NF 29). United States Pharmacopeia Convention, Rockville MD, 2010 (current from May 1, 2011 through July 31, 2011), pp 14-15. found at USP-NF Online (www.uspnf.com/uspnf)

Lacrimal fluid is isotonic with blood, having an isotonicity value corresponding to that of a 0.9% sodium chloride solution. Ideally, an ophthalmic solution should have this isotonicity value; but the eye can tolerate isotonicity values as low as that of a 0.6% sodium chloride solution and as high as that of a 2.0% sodium chloride solution without marked discomfort. However, any adjustment toward isotonicity by dilution with tears is negligible where large volumes of hypertonic solutions are used as collyria to wash the eyes; it is, therefore, important that solutions used for this purpose be approximately isotonic.

Reviewer Comment: The pH of the proposed drug product meets the USP <791> pH specification for purified water which is a range of 6.30-7.80. This is within the ophthalmic solutions range of 3.5 and 8.5 described above, and includes the ideal pH of 7.4 for normal tears. The sodium chloride concentration of the drug product solution is (b) (4)*, less than the 0.9% sodium chloride concentration of normal lacrimal fluid. However, the total osmolality of the drug product solution meets the required specification for isotonicity, as confirmed in a personal communication from the CMC reviewer on June 9, 2011.*[7]

4.2 Clinical Microbiology

No clinical microbiology studies were conducted or submitted to support this NDA. As part of their CMC submission materials, the sponsor provided data on microbiological colony forming units (CFU) counts and specifications from their stability batch testing. A clinical microbiology consult was requested by CMC pertaining to microbiological control, sterilization validation and sterility testing of the finished product.

The packaged product is sterilized at a contract facility by (b) (4) and the sterilization process is validated per (b) (4) suitable for a low bioburden process. The adequacy of the sterilization process validation will be assessed by the microbiology reviewer.

As of this date, the clinical microbiology review is pending.

4.3 Preclinical Pharmacology/Toxicology

The pharmacology/toxicology reviewer recommends approval of the application from the standpoint of pharmacology/toxicology. No nonclinical studies were conducted to support this NDA. However, this NDA does not require new nonclinical or clinical testing provided the (b) (4) does not change the chemistry specifications when comparing the (b) (4) products. According to the pharmacology/toxicology reviewer, "Upon testing, the product did not show different specifications when comparing the (b) (4) products. As a result, no nonclinical studies were required and none were submitted for this NDA."

[7] Ramaswamy, Muthukumar, personal communication (email), June 9, 2011.

According to the nonclinical reviewer, the only nonclinical concern relates to the impurities, degradants and leachables profile from containers/labels and closure systems. The sponsor addressed the concern as follows. Three separate lots of eyewash samples contained in two container systems (1 oz and 32 oz HDPE bottles) were tested [redacted] (b) (4) to determine if [redacted] (b) (4) had an impact on the level of leachables and degradants in the eyewash product. Purified water filled in plastic and glass bottles were used as controls. Bottles containing saline and borate buffer were used as test containers. No detectable change in the levels of saline or boric acid was noted in the tested samples.

The sponsor's leachables study indicated that [redacted] (b) (4) eyewash solutions contain known leachables below the detection limit and unknown leachables at <1 ppm level as recommended by FDA. The following chemicals were present below detection levels with the following detection limits: [redacted] (b) (4) No significant evidence of toxic byproducts was found. Concentrations of heavy metals were below the level of concern.

4.4 Clinical Pharmacology

No clinical pharmacology studies were conducted to support this NDA, and none are required.

5 Sources of Clinical Data

No clinical studies were conducted or submitted to support this NDA. FDA advised the sponsor at the September 2007 teleconference meeting that if the chemistry and microbiology sections of the NDA demonstrate the sterility of the product and no meaningful changes to the components after [redacted] (b) (4), then reference to the eyewash monograph could be used to support the NDA.

The sponsor relies on FDA's conclusion that the active ingredient is generally recognized as safe and effective for use as an eyewash as contained in the Ophthalmic Drug Products for Over-The-Counter Human Use final monograph (21 CFR §349). This application is a deviation from the OTC monograph only with respect to the lack of a preservative and the substitution of [redacted] (b) (4). The sponsor has provided the required certification to this effect.

5.2 Review Strategy

The sponsor's submission consists almost entirely of CMC information intended to demonstrate that the method of sterilization does not alter the product in any material way compared with existing eyewash products. Whether or not the CMC information is adequate will be a review issue, but the review team has determined that the submission is fileable.

This review will present information on the limited available adverse events safety data for the active ingredient purified water, other marketed OTC eyewash products, and the safety profile of the sponsor's marketed eyewash product containing a preservative.

See also the review by Dr. Jennifer D. Harris, M.D from the Division of Anti-Infective and Ophthalmology Drug Products (DAIOP), the specific subject matter review division (SSMRD) for this NDA. She recommends that the NDA be approved.

6 Review of Efficacy

Efficacy Summary

Clinical studies are not required to support this NDA. The drug product generally conforms to the requirements in 21 CFR §349 - Ophthalmic Drug Products for Over-The- Counter Human Use, Sec. 349.20 Eyewashes. Eyewash products which meet the regulatory requirements of §330.1 and §349.1 are recognized as being safe and effective and can be marketed OTC if there are no deviations from the established monograph.

This product deviates from the monograph in that it lacks a preservative agent. The product is labeled as single use only. An NDA is required under 21 CFR §310. (b) (4) because the method of ensuring product sterility is (b) (4), which is not allowed under the monograph.

The sponsor has filed an NDA deviation per 21 CFR §330.11. The sponsor has included the required statement in the NDA submission that the product meets all conditions of the applicable monograph except for the deviation for which approval is requested, and therefore may omit all information except that pertinent to the deviation.

6.1 Indication

The indication, "For cleansing the eye to help relieve irritation, (b) (4) burning, (b) (4) by removing loose foreign material, (b) (4) is compliant with the monograph (21 CFR §349.78) and is therefore acceptable.

Portions of the Ophthalmic Products for Over-the-Counter Human User final monograph (21 CFR §349) requirements follow.

§349.3 Definitions. (As used in this part):
(f) Eyewash, eye lotion, irrigating solution. A sterile aqueous solution intended for washing, bathing, or flushing the eye.

Subpart B — Active Ingredients

The active ingredient of the product is purified water. The product also contains suitable tonicity agents to establish isotonicity with tears, suitable agents for establishing pH and buffering to achieve the same pH as tears, and a suitable preservative agent.
[68 FR 7921, Feb. 19, 2003]

§349.78 Labeling of eyewash drug products.

(a) Statement of identity. The labeling of the product identifies the product with one or more of the following terms: “eyewash,” “eye irrigation,” or “eye irrigating solution.”

(b) Indications. The labeling of the product states, under the heading “Indications,” one of the following phrases:

(1) “For” (select one of the following: “flushing,” “irrigating,” “cleansing,” “washing,” or “bathing”) “the eye to remove” (select one or more of the following: “loose foreign material,” “air pollutants (smog or pollen),” or “chlorinated water”).

(2) “For” (select one of the following: “flushing,” “irrigating,” “cleansing,” “washing,” or “bathing”) “the eye to help relieve” (select one or more of the following: “irritation,” “discomfort,” “burning,” “stinging,” “smarting,” or “itching”) “by removing” (select one or more of the following: “loose foreign material,” “air pollutants (smog or pollen),” or “chlorinated water”).

(c) Warnings. In addition to the warnings in §349.50, the labeling of the product contains the following warnings under the heading “Warnings” for all eyewash products:

(1) “If you experience eye pain, changes in vision, continued redness or irritation of the eye, or if the condition worsens or persists, consult a doctor.”

(2) “Obtain immediate medical treatment for all open wounds in or near the eyes.”

(3) “If solution changes color or becomes cloudy, do not use.”

(d) Directions. The labeling of the product contains the following information under the heading “Directions”:

(1) For eyewash products intended for use with an eyecup. Rinse cup with clean water immediately before each use. Avoid contamination of rim and inside surfaces of cup. Fill cup half full and apply the cup to the affected eye, pressing tightly to prevent the escape of the liquid, and tilt the head backward. Open eyelids wide and rotate eyeball to ensure thorough bathing with the wash or lotion. Rinse cup with clean water after each use.

(2) For eyewash products intended for use with a nozzle applicator. Flush the affected eye as needed, controlling the rate of flow of solution by pressure on the bottle.

[53 FR 7090, Mar. 4, 1988, as amended at 68 FR 7921, Feb. 19, 2003]

A comparison of the characteristics of the proposed drug product with the requirements specified for OTC eyewash products in the final monograph shows the following concordant items:

- Drug product is a sterile, aqueous solution

- Active ingredient is purified water
- Contains a suitable isotonic agent to establish isotonicity with human tears
- Contains a suitable agent to establish pH and buffering capacity comparable to human tears
- Drug product is labeled as an ophthalmic solution
- Labeled indication matches §349.78 (b)(2)
- Labeling contains the warnings in §349.50 and §349.78(c)
- Packaging includes either nozzle applicator [§349.78(d)(2)] or eyecup [(§349.78(d)(1)] and required labeling directions

The only deviations from the monograph are the removal of a preservative and the use of [redacted] (b) (4) to serve the function of maintaining sterility during storage for this single use eyewash product.

7 Review of Safety

Safety Summary

Clinical studies are not required to support safety for this NDA for the reasons outlined in the section 6 Efficacy Summary above.

The inactive ingredients in the proposed drug formulation are listed in the United States Pharmacopeia (USP) or National Formulary (N.F.) and conform to their specifications. The sponsor has provided study data to demonstrate there are no significant concentrations of toxic degradants or leachables generated by the [redacted] (b) (4) process during manufacture which may pose a safety risk.

The sponsor has marketed more than [redacted] (b) (4) units of a comparable sterile eyewash, largely in Canada, since 2003 and received no reports of adverse effects. There have been no serious adverse event reports. There have been no product recalls. Limited data from the FDA AERS database for the active ingredient (purified water) and for other marketed OTC eyewash products have a benign safety profile, with rare reports of any adverse events over a period of more than 25 years. No significant safety hazards associated with these products have been identified in readily available published studies.

This single use sterile product is not expected to pose any serious safety risk to consumers so long as product sterility is ensured during manufacture, and the [redacted] (b) (4) method is shown effective in maintaining product sterility for the proposed shelf life period. These are critical issues for the CMC and microbiology reviewers, and NDA approval will depend on a positive determination for these points.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Not Applicable

7.6.2 Human Reproduction and Pregnancy Data

Not Applicable

7.6.3 Pediatrics and Assessment of Effects on Growth

The application does not trigger PREA as it is not for a new active ingredient, dosage form, indication, route of administration or dosing regimen.

The information submitted by the Sponsor in the pediatric section of the NDA submission stated the pediatric administrative information required under 21 CFR §314.50(d)(7) and the Pediatric Research Equity Act (PREA) is not applicable. Niagara Pharmaceuticals, Inc. eyewash product is labeled as required by 21 CFR Subpart C §201.66 and under the United States monograph 21 CFR §349.20 Eyewashes.[8]

On January 6, 2011 by email the PMHS staff agreed that the proposed product does not trigger PREA. Further, as the product submission is not a response to a PREA PMC, the application does not require PeRC review. The required Pediatric Page for this drug product has been filed in DARRTS.

7.7 Additional Submissions / Safety Issues

The original product name when the sponsor filed PIND 77,883 was [redacted] (b) (4)

FDA later advised the sponsor in the "refuse to file" letter for NDA 22-305 (item 21):

> "If you reference the Ophthalmic Drug Products for Over-the-Counter Human Use monograph (21 CFR §349) for eyewash products to support your application, your drug product cannot be called [redacted] (b) (4)
>
> [redacted] (b) (4)

The sponsor has removed the reference to [redacted] (b) (4) in its resubmission.

[8] NDA 22-305, Module 1, volume 1.1, section 1.9, p. 15, November 1, 2010.

There is a discrepancy between the revised labeling and portions of Module 2 of the current submission. For example, the Quality Overall Summary Introduction states:

(b) (4)

Similarly, the sponsor's Proposed indication in Module 2 differs from that given in the revised labeling submitted:

"For cleansing the eye to help relieve irritation, (b) (4) burning, (b) (4) by removing loose foreign material (b) (4)

The Drug Facts labeling language submitted by the sponsor is entirely correct and supported by the final monograph. The highlighted portions of the language in the Module 2 quotations are not acceptable for OTC approval under the monograph, and would require clinical data to support their use in an NDA.

Reviewer Comment: These two examples are related to the (b) (4) *eyewash indication issue FDA previously addressed with the sponsor. To be clear, the sponsor is not asking for language related to treating chemical burns in the official labeling section of this NDA. For purposes of NDA review, the submitted Drug Facts labeling is quite acceptable on this point. We have not called the discrepancy between proposed labeling and the language in Module 2 to the sponsor's attention. This reviewer recommends that an addendum to an approval letter to the sponsor restate the distinction between the final eyewash monograph* (b) (4)

8 Postmarket Experience

8.1 Sponsor's Eyewash with Preservative

The proposed new product formulation sterilized by (b) (4) is not currently marketed. However, the company has marketed a similar eyewash product in Canada, which differs from the proposed product only in that it contains a preservative. See table below. The original formulation is not marketed in any countries other than Canada and the drug has not

[9] NDA 22-305, Module 2.3, p.3, November 1, 2010
[10] NDA 22-305, Module 2.3, p.3, November 1, 2010

been withdrawn from marketing for any reason relating to the safety and effectiveness. There are no other countries in which applications are pending.

Table 2: Sponsor's Canadian Eyewash Product Ingredients

Ingredient name	Active/Inactive	CAS#	%
Purified Water	Active	N/A	97%
Boric Acid	Inactive	10043-35-3	(b) (4)
Sodium Borate	Inactive	1330-43-4	
Sodium Chloride	Inactive	7647-14-5	
Disodium Edetate	Inactive	6381-92-6	
Benzalkonium Chloride	Inactive	68424-85-1	
Benzethonium Chloride	Inactive	121-54-0	

Source: NDA 22-305 Submission, 120-Day Safety Update, p.4, March 11, 2011.

The following safety information provided by the sponsor is based on data for the original formulation, (b) (4) From June 3, 2003 through November 25, 2010 approximately (b) (4) units were sold in the United States and Canada. As of the spring of 2007 all units sold were in Canada, because an NDA was being filed in the United States. However, prior to that time about (b) (4) units were sold in the United States.

From June, 2003 to the time a repeat FDA inspection was conducted in September, 2010, no adverse events have been reported to the sponsor. No product recalls have occurred during this time. This information was reviewed at the FDA inspections in 2006 and again in September, 2010.

In 2008, a complaint was received by Health Canada regarding the "yellowness of the Eyewash solution." According to the sponsor, this yellowing was determined to be a routine function of all (b) (4) substances. Independent testing by Health Canada showed that the product samples tested passed the prescribed specifications. It was also determined that the complainant was a salesman from a competitor. The complaint was dismissed as being "without merit."

8.2 FDA AERS Adverse Event Case Reports

The sponsor did not provide any analysis of FDA AERS reports. This reviewer performed searches in FDA AERS database on multiple occasions using the terms "Niagara", "Niagara Pharmaceuticals", "eyewash", and "eye wash" in various AERS search fields with no positive results.

This reviewer conducted an updated search in AERS on May 27, 2011 for all adverse events for the drug product term "Collyrium."[11] A total of seven case reports were identified. None of the case reports included a narrative. All cases were reported from the United States. The case report

[11] Collyrium for Fresh Eyes is an OTC monograph compliant eyewash product marketed by Bausch & Lomb, Inc.

dates ranged from 1984 to 1997. There were 4 cases reported in males and 3 in females, and the reported ages of the cases were from 29-76 years of age. Four of the cases reported serious adverse events. One case reported an outcome of hospitalization (bullous dermatitis, eye pain). One case reported an outcome of disability (eye pain, facial edema, visual impairment). One case reported outcomes of a life threatening event and disability (chest pain, dyspnea, paresthesia, vasodilatation) in a 40 year old male with concurrent exposure to Ophthaine HCl. No common demographic characteristics were noted among this small number of cases. Assessment of causality without any case narratives is problematic. The cases might be confounded by indication, among other biases, but no information is available from the ISR's to support such an analysis.

Most of the adverse events associated with these seven case reports were localized: conjunctivitis (3 cases), eye pain (3 cases), facial edema (2 cases), amblyopia (1 case), application site reaction (1 case), visual impairment (1 case), and corneal lesion (1 case).

This reviewer conducted another updated search in AERS on May 27, 2011 for all adverse events for the drug product term "purified water." A total of seven case reports were identified. There was no overlap between the cases found in the AERS search for "Collyrium" and the AERS search for "purified water." Four of the cases reported were from the United States with one case each from Great Britain, Mexico, and Thailand. The case report dates ranged from 1996 to 2010. There were 4 cases reported in males and 3 in females, and the reported ages of the cases were from 24-79 years of age. No common demographic or other features among this small number of cases were noted. Most cases clearly were unrelated to possible drug toxicity due to topical exposure to purified water, or were confounded by pre-existing medical conditions, concomitant drug exposures, and non ophthalmic use.

Reviewer Comment: The striking feature of these AERS search results is the relative paucity of adverse event case reports for either eyewash products or the active ingredient purified water. No estimates of sales figures for these products are known. The sponsor has stated they have marketed more than (b) (4) *units of their product since 2003. Collyrium has been marketed since at least 1984. There are no unequivocal case reports of serious adverse events for eyewash products in the AERS database, dating back at least 25 years. Nor are there any instances of systemic adverse events likely to be related to topical exposure to these products, despite millions of consumer exposures. The very limited data in AERS described here lends support for the safety of OTC eyewash products available under the final monograph.*

One AERS case report from the U.S. is described in more detail below.

(AERS Case 6535255) The case was reported from the U.S. on April 10, 2008. A 25 year old used Collyrium Eye Wash for 1 day. Adverse events reported for this case were chemical burns of the eye, eye irritation, and increased lacrimation.

A mother reported that her 25-year-old son experienced eye irritation, watering eyes, eye stinging, and burns around both pupils while using Collyrium Eye Wash. She stated that during

the evening of (b) (6), her son administered Collyrium Eye Wash to both eyes and at some point thereafter, inserted his contact lenses into both eyes. She stated, "That's when his eyes began to feel irritated and watery. All night long his eyes were irritated and watery." In the morning on (b) (6), the mother took her son to the hospital emergency room where the staff washed his eyes out and added drops (unspecified solutions) to take away the sting, but nothing helped. Therefore, a gel was administered to both eyes and his eyes were examined under a slit lamp. They found a perfect circle around both pupils and informed the mother these were burns. Dilating drops were also administered to the son's eyes while at the emergency room. After three hours in the emergency room the son was sent home with four unspecified prescriptions including a "strong pain medication." Later, on (b) (6), the son flew home to Florida.

"On 12/31/2007, he missed work and couldn't drive, as his eyes were dilated." He also had to wear sunglasses due to the dilation. On 12/31/2007, the son consulted an eye specialist who confirmed the diagnosis of "a strong burn in both eyes." The specialist prescribed an unspecified steroid drop for relief, which worked. The mother stated that her son was feeling better by 01/01/2008.

A quality investigation was conducted and the batch record review indicated that the product was manufactured per global and local product specifications. All quality inspections met acceptance criteria. Compounding processes for the referenced lot were reviewed and found to have been performed properly. In-process and final product chemistry testing as well as sterility results met specifications. There were no process issues noted with the manufacturing of this batch that would relate to a report of this nature. Environmental monitoring data obtained during the filling of this lot were within specifications. The analysis of the retain unit found that the product met stability limits for all parameters tested. Lastly, analysis of the complaint sample by chemistry found that the sample met stability limits for all parameters tested.

Reviewer Comment: This case was reported by a consumer and described apparent chemical burns with concurrent use of contact lenses and Collyrium branded OTC eyewash product. No further information about why the consumer used the eyewash is available. The adverse events resolved in three days with topical steroid eye drops treatment without apparent sequelae. A quality investigation by the manufacturer did not reveal any manufacturing or product quality issues for the implicated drug lot. There is a possible causal relationship with exposure to an OTC eyewash drug product, confounded by mechanical exposure to contact lens wear. See further comment about a published case report which bears some similarities in Section 9.1 below.

9 Appendices

9.1 Literature Review/References

The sponsor did not provide any references or perform a literature search concerning the safety of topical eyewashes, or the drug active ingredient, purified water. This reviewer performed a number of Medline searches to identify relevant papers.

The terms “eyewash” and “eye wash” yielded a total of 47 citations in PubMed on May 27, 2011. Each of the abstracts was reviewed. There were three papers of possible relevance.

None of the three publications provides direct evidence for a safety hazard related to the applicant’s proposed product. The literature search did not provide significant evidence of safety hazards due to sterile eyewash solutions when used as directed, except when the drug product itself has become contaminated.

The first publication is a 1983 case report.[12] As reported by the authors, during a routine ophthalmologic examination, an aphakic soft contact lens was accidentally soaked in eyewash (Blinx-Barnes Hind) instead of contact lens storage solution. At the completion of the examination, about 30 minutes later, the soft contact lens was placed in the patient's eye. The patient tolerated the contact lens for approximately one hour but the pain and photophobia then became intolerable. The patient removed the contact lens and called his ophthalmologist.

The next day the patient's best corrected visual acuity was *20/200*. Pseudoptosis was associated with eyelid edema, conjunctival chemosis, and corneal edema that included folds in Descemet's membrane. The intraocular pressure was normal. Trace cells and flare were present in the anterior chamber of the involved eye. Chemical keratoconjunctivitis secondary to eyewash was diagnosed and the patient was treated with corticosteroid eyedrops. Approximately three days after the episode the patient's visual acuity had improved to *20/25* and external eye had returned to normal.

The involved eyewash contained boric acid and sodium borate with phenylmercuric acetate 0.004% added as a preservative. This irrigating solution is designed for use with fluorescein ophthalmic strips. Although the label cautions, "Do not use while lenses are in the eye," it is used as an eyewash or irrigating solution. Most rinsing and storage solutions consist of sterile preserved saline solution.

A second publication (letter) described the onset of blindness in a patient using a home manufactured antibiotic eyewash.[13] The patient was a 46 year old man living in Gabon. In May 1997 he suffered from irritation of his eyes. He attended a general hospital in Gabon, where he was provided with penicillin and tetracycline in powder form, to mix in boiled water and to use as an eyewash. It was very painful and he lost his vision. He came to the eye clinic at Enongal, Cameroon (the closest eye department) on 10th November 1997. On examination, the patient’s visual acuity was found to be: Right (OD)- no perception of light; Left (OS)- hand movements. The cornea of the right eye was completely scarred. In the left eye there was a thick scar of the upper cornea while the lower cornea was clear. There were many posterior synechiae and a dense cataract in the left eye.

[12] Flach AJ, Sorenson JA. Eyewash mistaken for contact lens soaking solution. Am J Ophthalmol. Jun;95(6):850-1. 1983.
[13] Stagles M, Ekotto JJ, Nkoum S. Blindness provoked by locally-produced antibiotic eyewash. Community Eye Health. 12(31):48, 1999.

The authors opined that the eyewash was very hypertonic and alkaline, and was the source for the ocular injury. They emphasized the need for care and precision in the local production of topical eye medicines.

The third publication reports a study conducted to investigate the frequency of bacterial contamination of multidose proparacaine hydrochloride, tropicamide, and eyewash bottles used in veterinary ophthalmology examination rooms at Purdue University during normal operating procedures. [14]

Three representative bottles each of proparacaine hydrochloride, tropicamide, and purified water eyewash were opened at the same time, numbered, and placed into small animal examination rooms. Doctors, students and technicians who were using the solutions were blinded to the study. Aerobic cultures were obtained at the time of opening (time 0), at 1 week (time 1), and at 2 weeks after opening (time 2) the bottles. The sites cultured included a drop of each solution, the inside of the bottle cap, the tip of the bottle, and the bottle threads and medication residue found in these threads.

The standard purified water eyewash (Eye wash sterile eye irrigating solution, Major Pharmaceuticals, Livonia, MI, USA) contained preservatives edetate disodium 0.025% and sorbic acid 0.1% to prevent bacterial contamination. The product insert for the eyewash suggests avoidance of touching the bottle tips to ocular and environmental surfaces in order to prevent contamination, and discarding the solutions if cloudiness or discoloration is seen.

Aerobic cultures of tropicamide and proparacaine had no growth of bacteria from any of the evaluated sites. *Staphylococcus epidermidis* was cultured from the tip of one bottle of eyewash after 1 week. At week 2, aerobic cultures of the tip of the same bottle were negative. Only 1/108 cultures were positive over a 2-week time period (four sites for each solution at three sampling times).

The authors conclude that multiuse proparacaine, tropicamide, and eyewash solutions used in veterinary examination have a low level of bacterial contamination 1 or 2 weeks after opening when used and stored according to the recommendations of the product manufacturers and previous studies.

A PubMed search for the conjoint terms “purified water” and “adverse events” yielded two citations, neither of which was relevant.

Reviewer Comment: The rarity of readily identifiable publications about safety hazards associated with topical eyewash products is consistent with the lack of significant numbers of

[14] Betbeze CM, Stiles J, Krohne SG. Assessment of bacterial contamination of three multidose ophthalmic solutions. Vet Ophthalmol. Mar-Apr;10(2):81-3. 2007.

reports in FDA AERS database, despite the widespread use of these products over decades. It provides further support that OTC eyewash products marketed under the final monograph are safe and effective.

The case description of chemical keratoconjunctivitis in the case report by Flach (1983) bears a number of similarities to the AERS case (6535255) described in Section 8.2 above. Both involve the use of a sterile eyewash product by a patient or consumer wearing contact lenses. Comparative details are not complete. There is no information about whether the AERS case wore soft contact lenses; eyewash was not topically applied to the eyes of the patient reported by Flach. The preservative used in Collyrium is benzalkonium chloride (0.01%) versus the phenylmercuric acetate 0.004% used for that purpose in the Blinx-Barnes Hind eyewash. Both cases apparently resolved without permanent sequelae after specialist treatment in a few days time.

Nonetheless, the parallels suggest there is a potential interaction between some contact lenses and the use of sterile eyewash containing preservatives. The sponsor's product has been reformulated to remove chemical preservatives, but may contain some low level (<1ppm) degradants from (b) (4) *. It is not clear if information from these two cases is sufficient to support a labeling warning to consumers wearing contact lenses when using eyewash products. If so, the warning might best be applied to all OTC monograph eyewashes containing preservatives. Based on available information, a specific warning for this product does not appear warranted.*

9.2 Labeling Recommendations

The sponsor proposed the proprietary trade name (b) (4) with the alternate name Pur-Wash. A web search revealed a number of existing products named (b) (4). Among them is a similar composition eyewash solution made in UK (since 1994). There is also a waterless hand sanitizer gel (alcohol based), and a disinfecting liquid hand soap (with trichlorosan). After evaluation, DDMAC found the name (b) (4) to be unacceptable. On further review, DMEPA determined the alternate name Pur-Wash (Purified Water) Ophthalmic Solution was acceptable on June 6, 2011.

As outlined above in Section 6.1 Indication, the sponsor's proposed revised product labeling is consistent with that for OTC products under the final monograph. The required warnings have been included in acceptable Drug Facts format. Appropriate directions are provided for the two different closure types for this product; nozzle and sterile eyecup.

The sponsor's directions for use of the nozzle closure are identical to those found at 21 CFR §349.78(d). The sponsor has provided an eyecup with a modified design, which includes a central multiple-opening orifice and two vent ports to allow continuous solution flow to the eyecup and excess fluid to drain from the vents during flushing. The sponsor has provided directions suitable for its modified eyecup design.

The directions for use of an eyecup under 21 CFR §349.78 (d) state:

> "Rinse cup with clean water immediately before each use. Avoid contamination of rim and inside surfaces of cup. Fill cup half full and apply the cup to the affected eye, pressing tightly to prevent the escape of the liquid, and tilt the head backward. Open eyelids wide and rotate eyeball to ensure thorough bathing with the wash or lotion. Rinse cup with clean water after each use."

The sponsor's proposed directions are:

(b) (4)

Reviewer Comment: The directions for the sponsor's eyecup are appropriate for use with their modified eyecup design, which allows repeated flushing with fresh eyewash solution by pressure on the container without having to refill the eyecup during use, and appears to function, as a practical manner, similarly to a nozzle closure. The modified directions are also more consistent with the single use labeling of the product, while the monograph directions imply the eyecup may be reused. This reviewer believes the sponsor's proposed eyecup directions should be permitted.

The proposed Drug Facts labeling contains the following warnings and the label conforms to CFR §349.50 and §349.78(c) requirements:

- 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.
- Obtain immediate medical treatment for all open wounds in or near the eyes
- If solutions changes color or become cloudy do not use
- Do not use on broken skin
- Stop using eye wash and ask a doctor if you experience an open wound near the eyes
- To avoid contamination, do not touch tip of container to any surface.
- Do not reuse. Once opened, discard any remaining product.

All container sizes include a tamper evident seal and labeling instructions not to use the product if it is broken. Product labeling includes directions to discard any remaining product after a single use, which is necessary since there is no means to ensure product sterility once the product container is opened.

The original product Drug Facts label submitted with this NDA included a statement restricting (b) (4) . FDA advised the sponsor in an advice letter there was no evidence to support this age limit, and the sponsor has submitted revised labeling removing this statement.

The sponsor has added a revised product statement on the PDP "Sterile (b) (4) Solution." This reviewer doubts that the term (b) (4) conveys meaningful information to a consumer about the product or its qualities, and recommends that this term be deleted. As the DMEPA reviewer pointed out at the review team wrap-up meeting on June 13, 2011, the tamper evident seal is overprinted with (b) (4) English phrases. He recommended that the sponsor replace this with a seal printed only in English. This reviewer agrees.

This reviewer has no further suggestions to make about the proposed Drug Facts labeling and recommends approval as revised.

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

VICTOR ALEXANDER
06/23/2011

LESLEYANNE A FURLONG
06/23/2011
I concur with Dr. Alexander's recommendation for approval from a clinical perspective.

CLINICAL REVIEW

Application Type	505(b)(2)
Application Number(s)	NDA 22-305
Priority or Standard	Standard
Submit Date(s)	February 24, 2008, October 29, 2010
Received Date(s)	February 26, 2008, November 01, 2010
PDUFA Goal Date	September 01, 2001
Division / Office	
Reviewer Name(s)	Jennifer D. Harris, M.D.
Review Completion Date	3/23/2011
Established Name	Purified water 98.3%
(Proposed) Trade Name	Eyewash
Therapeutic Class	
Applicant	Niagara Pharmaceuticals, Inc.
Formulation(s)	Ophthalmic solution
Dosing Regimen	Flush eye as needed
Indication(s)	For cleansing the eye to help relieve irritation, (b) (4) burning, (b) (4) by removing loose foreign material, (b) (4)
Intended Population(s)	

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

NDA 22-305 Eye Wash is recommended for approval for cleansing the eye to help relieve irritation, (b) (4) burning, (b) (4) by removing loose foreign material, (b) (4).

1.2 Risk Benefit Assessment

The product quality information submitted in this NDA support the fact that the attributes of the proposed drug product do not deviate from the over-the-counter (OTC) monograph after (b) (4) *other than the fact that the product does not contain an antimicrobial preservative. A preservative agent should not be required since the product is exclusively a single use product and the entire volume is expected to be used. The risk/benefit of eyewash products has been established for products that follow the OTC monograph.*

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

N/A – there are no postmarketing recommendations for this product.

1.4 Recommendations for Postmarket Requirements and Commitments

N/A – there are no postmarketing recommendations for this product.

2 Introduction and Regulatory Background

NDA 22-305 was originally submitted on January 30, 2008, for Niagara Pharmaceuticals, Inc. eyewash product. The application received a refuse-to-file response on April 25, 2008, due to various deficiencies in the application package. The application was resubmitted for review on November 1, 2010.

Eyewash products which meet the regulatory requirements of §330.1 and §349.1 are recognized as being safe and effective and can be marketed as OTC if there are no deviations from the established monograph. The current product requires a New Drug Application since it deviates from the OTC monograph for eyewash products and it is sterilized via (b) (4). *The product does not contain a preservative as required per the monograph and the final sterilization* (b) (4).

Drugs sterilized by (b) (4) are considered new drugs by the Agency and require a New Drug Application prior to marketing per §310.(b) (4).

This NDA should not require any preclinical or clinical testing of this product provided that the (b) (4) does not add anything to the product. Niagara has submitted a report entitled "Study on the Impact of (b) (4) on Eye Wash Product and container Systems" to Demonstrate the Effect of Sterilization with (b) (4).

2.1 Product Information

Name: Eyewash
Actives: purified water USP (98.3%)
Inactives: boric acid (b) (4), sodium chloride (b) (4) sodium borate (b) (4)

2.2 Tables of Currently Available Treatments for Proposed Indications

There are several eyewash products currently being marketed under the OTC monograph. This is the only NDA to date for this indication.

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient is purified water which is readily available.

2.4 Important Safety Issues With Consideration to Related Drugs

None.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

See section 2.0.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

Clinical studies are not required to support this NDA.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The applicant has submitted a study for leachables in their eyewash product arising from the packaging components and degradants due to (b) (4) used for sterilization of their product. The study targets the borate and chloride degradants and leachables from two different containers with labels (32oz and 1 oz HDPE) containing three different lots of the eye wash products. (b) (4) purified water in a 32 oz HDPE bottle and a (b) (4) Eye Wash product sample in a 32 oz amber glass bottle were used as controls for the leachables study.

Validated analytical methods (GC/MS and IC/Cond) were used to screen for leachable components and degradants. The submitted report details the results of analysis of three lots of eyewash product in the two container systems (b) (4). The effect of storage time on degradants and leachables in (b) (4) samples was also analyzed in the accelerated stability study at 40°C/75%RH on the six (b) (4) samples.

Borate, Chloride and Degradants

Sample	Borate, (b) (4)		Chloride, % Cl^-		Total Degradants/ Impurities, µg/mL
	(b) (4)	% Change	(b) (4)	% Change	(b) (4)
32oz HDPE, Lot# 10NP0005	(b) (4)				
32oz HDPE, Lot# 10NP0007					
32oz HDPE, Lot# 10NP0008					
1oz HDPE, Lot# 10NP0005					
1oz HDPE, Lot# 10NP0007					
1oz HDPE, Lot# 10NP0008					

Reviewer's comments: *There was no significant change in the borate, chloride or degradants observed in the drug product* (b) (4).

Borate at Zero, Three and Six Months Time Point 40°C/75%RH

Sample	Borate, (b) (4)				(b) (4)	(b) (4)
	(b) (4)				(b) (4)	% Change After 6 Months	R^2
	T=0	1 month	3 months	6 month		
32oz HDPE, L# 10NP0005						
32oz HDPE, L# 10NP0007						
32oz HDPE, L# 10NP0008						
1oz HDPE, L# 10NP0005						
1oz HDPE, L# 10NP0007						
1oz HDPE, L# 10NP0008						

Chloride at Zero, Three and Six Months Time Point 40°C/75%RH

Sample	Chloride, % Cl^- (b) (4)					
	(b) (4)			(b) (4)	% Change After 6 Months	R^2
	T=0	1 month	3 months	6 month		
32oz HDPE, L# 10NP0005						(b) (4)
32oz HDPE, L# 10NP0007						
32oz HDPE, L# 10NP0008						
1oz HDPE, L# 10NP0005						
1oz HDPE, L# 10NP0007						
1oz HDPE, L# 10NP0008						

Degradants at 0 to Three Months Time point 40°C/75%RH

Sample	Total Degradants/Impurities (µg/mL)
	(b) (4) (b) (4)
32oz HDPE, Lot# 10NP0005	(b) (4)
32oz HDPE, Lot# 10NP0007	
32oz HDPE, Lot# 10NP0008	
1oz HDPE, Lot# 10NP0005	
1oz HDPE, Lot# 10NP0007	
1oz HDPE, Lot# 10NP0008	

Reviewer's comments: *There was no significant change in the borate, chloride or degradants observed in the drug product during the six months of stability testing after* (b) (4)

Leachables

During development and validation of the GC/MSD method for extractables and leachables from Niagara container systems, ten potential leachables were identified:

(b) (4)

There were no known or unknown leachables found in the (b) (4) eye wash samples. There were no known or unknown leachables found in the (b) (4) samples (purified water in 32oz HDPE and eye wash product in 32oz glass). There were no known or unknown leachables found in the (b) (4) eye wash samples during the 6 months of stability at 40°C/75%RH.

4.2 Clinical Microbiology

N/A – this is not an anti-infective product.

4.3 Preclinical Pharmacology/Toxicology

Nonclinical studies are not required to support this NDA.

4.4 Clinical Pharmacology

Clinical studies are not required to support this NDA.

5 Sources of Clinical Data

Clinical studies are not required to support this NDA.

6 Review of Efficacy

Clinical studies are not required to support this NDA. Efficacy is supported by the OTC monograph.

7 Review of Safety

Clinical studies are not required to support this NDA. Safety is supported by the OTC monograph.

8 Postmarket Experience

N/A – this product is not currently marketed.

9 Appendices

9.1 Labeling Recommendations

(b) (4)

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

JENNIFER D HARRIS
05/04/2011

WILLIAM M BOYD
05/04/2011

WILEY A CHAMBERS
05/10/2011

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 22-305 **Applicant: Niagara Pharmaceuticals, Inc.** **Stamp Date: 11/01/2010**

Drug Name: Eye Wash (Purified Water USP) **NDA/BLA Type: 505(b)(2)**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				Paper Label (electronic)
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?			X	
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			Submitted after IR 11/17/2010
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			Submitted after IR 11/17/2010
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			Submitted after IR 11/17/2010
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Submitted after IR 11/17/2010
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(2) Purified Water USP
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?			X	Relies on Monograph GRASE status of RLD

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			Submitted after IR 11/17/2010
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			Submitted after IR 11/17/2010
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?			X	
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*,			X	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	label comprehension, self selection and/or actual use)?				
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			X	
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
34.	Are all datasets to support the critical safety analyses available and complete?			X	
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?			X	No clinical studies. Not needed
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			X	

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __YES__

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Initial Submission did not contain required safety update (Module 5) and summaries (Module 2). IR sent 11/17/2010. Sponsor replied with necessary infomation on 11/29/2010.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Victor Alexander, MD, MSPH	December 20, 2010
Reviewing Medical Officer	Date
Lesley-Anne Furlong, MD	December 20, 2010
Clinical Team Leader	Date

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

/s/

VICTOR ALEXANDER
12/22/2010
MO FIling review

LESLEYANNE A FURLONG
12/22/2010

CLINICAL FILING CHECKLIST FOR NDA 22-305

NDA/BLA Number: 22-305 **Applicant: Niagara Pharmaceuticals, Inc.** **Stamp Date: 11/01/2010**

Drug Name: Eye Wash **NDA Type: 3**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				Mixed-Paper/Electronic
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?			X	Clinical studies not performed
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?			X	
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?			X	
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?			X	
9.	Has the applicant submitted the integrated summary of safety (ISS)?			X	
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	
11.	Has the applicant submitted a benefit-risk analysis for the product?			X	
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(2)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication:			X	

CLINICAL FILING CHECKLIST FOR NDA 22-305

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?			X	
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?			X	
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA 22-305

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			X	
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
34.	Are all datasets to support the critical safety analyses available and complete?			X	
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?			X	
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			X	

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___Yes___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR NDA 22-305

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None

Reviewing Medical Officer	Date
Clinical Team Leader	Date

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

/s/

JENNIFER D HARRIS
12/17/2010

WILLIAM M BOYD
12/17/2010

NDA 74-Day Fileability Meeting Checklist

NDA#: **22-305**
Product Name: **(b) (4) Eye Wash**
Sponsor: **Niagara Pharmaceuticals**
Reviewer: **Joseph Porres**
Date: **4/18/2008**

Item	Yes	No
1. Is the clinical section of the NDA organized in a manner to allow substantive review to begin?		**X**
2. Is the clinical section of the NDA indexed and paginated in a manner to allow substantive review to begin?		**X**
3. Is the clinical section of the NDA legible so that substantive review can begin?	**NA**	
4. If needed, has the sponsor made an appropriate attempt to determine the most appropriate dosage and schedule for this product through appropriately designed dose-ranging studies?	**NA**	
5. Do there appear to be the requisite number of adequately and well-controlled studies in the application?		**X**
6. Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling?		**X**
7. Are all data sets for pivotal efficacy studies complete for all indications requested?		**X**
8. Do all pivotal studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?		**X**
9. Has the applicant submitted line listings in a format to allow reasonable review of the patient data and in the format agreed to previously by the Division?		**X**
10. Has the application submitted a rationale for the applicability of foreign data (disease specific, microbiologic specific) in the submission to the U.S. population?	**NA**	
11. Has the applicant submitted all additional required case record forms, in addition to deaths and drop-outs, previously requested by the Division?	**NA**	
12. Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously agreed to by the Division?		**X**
13. Has the applicant presented the safety assessment based on all current world-wide knowledge regarding this product?		**X**
14. Has the applicant submitted adequate and well-controlled actual usage trial(s) within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?		**X**
15. Has the applicant submitted adequate and well-controlled labeling comprehension trial(s) within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	**NA**	
16. Has the applicant submitted draft labeling consistent with 201.5 and 201.56, current divisional policies, and the design of the development package?		**X**
17. Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?		**X**
18. Has PREA been addressed?		**X**
19. From a clinical perspective, is this NDA file-able? In no, please explain below.		**X**

Reviewer Comments:
This NDA is for an eye wash that is now sterilized by [redacted]. Under U.S. regulations (21 CFR [redacted] all drugs that are [redacted], which would include this over-the-counter eye wash, require a New Drug Application.

At the PIND meeting, FDA stated that if a review of the chemistry and microbiology sections demonstrate sterility of the product and no meaningful chemistry changes to the components after [redacted] then the sponsor could make reference to the monograph to support the NDA. However, multiple deficiencies in the chemistry and microbiology sections have been found in the submission that trigger the need for clinical safety and efficacy studies. The submitted NDA lacks any safety and efficacy studies and, therefore, the submission is incomplete and that leads to the refusal to file action.

Medical Officer
Division of Over-the-Counter Drug Products

Medical Team Leader
Division of Over-the-Counter Drug Products

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

/s/

Joseph Porres
4/18/2008 08:24:39 AM
MEDICAL OFFICER

Bindi Nikhar
4/18/2008 08:28:06 AM
MEDICAL OFFICER
Concur. This NDA is to have a Refusal-to-File action.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 22-305 **Applicant: Niagara Pharmaceuticals, Inc.** **Stamp Date: February 26, 2008**

Drug Name: Purified Water, USP **NDA/BLA Type:**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				Paper CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?			X	No clinical section
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?			X	
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?			X	Paper submission
5.	Are all documents submitted in English or are English translations provided when necessary?			X	
6.	Is the clinical section legible so that substantive review can begin?			X	
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?			X	
9.	Has the applicant submitted the integrated summary of safety (ISS)?		X		No clinical section
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?		X		
11.	Has the applicant submitted a benefit-risk analysis for the product?			X	
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(2) – purified water, USP (application should reference the monograph)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:				
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1			X	

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Indication: Pivotal Study #2 Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?			X	
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?			X	
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested			X	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	by the Division)?				
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			X	
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
34.	Are all datasets to support the critical safety analyses available and complete?			X	
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?			X	
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			X	

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? From a clinical perspective, the application is not filable. No clinical studies have been conducted for this application.

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

The final product does not meet the monograph requirements for eye wash products after (b) (4). The applicant has not provided adequate clinical information for review to evaluate the risks/benefits of this deviation from the monograph.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Jennifer Harris, M.D.	4/10/08
Reviewing Medical Officer	Date
William Boyd, M.D.	
Clinical Team Leader	Date

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

/s/

Jennifer Harris
4/15/2008 03:33:22 PM
MEDICAL OFFICER

William Boyd
4/16/2008 06:11:22 AM
MEDICAL OFFICER