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RESEARCH**

*APPLICATION NUMBER:*

**022305Orig1s000**

**OTHER REVIEW(S)**

# 3rd Addendum Labeling Review for Pur-Wash Eyewash Ophthalmic Solution

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**SUBMISSION DATES:** August 29, 2011

**NDA/SUBMISSION TYPE:** N22-305

**ACTIVE INGREDIENTS:** Purified water USP 98.3%

**DOSAGE FORM:** Ophthalmic solution

**SPONSOR:** Niagara Pharmaceuticals, Inc. (NPI)  
60 Innovation Dr.  
Flamborough, Ontario L9H 7P3  
Canada

Robert Schiff (agent)  
Schiff & Company  
(973) 227-1830

**REVIEWER:** Elaine Abraham

**TEAM LEADER:**

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## I. BACKGROUND

Labeling recommendations for Pur-wash Eyewash (98.3% purified water) ophthalmic solution were emailed to the sponsor on August 25, 2011. Revised labeling was submitted on August 29, 2011.

<b>Submitted Labeling</b>	<b>Representative of Following SKUs</b>
1 fl. oz. (30 mL) bottle	N/A
4 fl. oz. (118 mL) bottle	N/A
8 fl. oz. (236 mL) bottle	N/A
16 fl. oz. (473 mL) bottle ( horizontal layout)	N/A
16 fl. oz. (473 mL) bottle ( vertical layout)	N/A
32 fl. oz. (946 mL) bottle	N/A

## II. REVIEWER'S COMMENTS

The sponsor was provided with the following labeling comments on August 25, 2011:

1. **1 fl. oz. size Warnings** - “For external use only” cannot be placed on the same line as the **Warnings** heading and should be moved to the next line [see 21 CFR 201.66(d)(6)]. This is true even when using the modified format under 21 CFR 201.66(d)(10). The “Do not use” subheading should be moved to the line below the **Warnings** heading and “For external use only” statement so that “Do not use” is associated with the bulleted statements that follow. The bulleted statement, “if you experience any open wounds...” can follow on the same line. A hairline should precede the “Do not use” subheading. The phrase “For external use only” should be in the same type size as used for the text in the label and should be bolded, but not italicized, so as not to diminish the prominence of the **Warnings** heading.

The format below should be followed:

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**Warnings**

**For external use only**

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**Do not use** ■ if you experience any open wounds...

*Reviewer’s comment: The revised labeling follows the format above and is acceptable.*

2. **1 fl. oz. size annotated specifications for Drug Facts** - Clarify the type size for the **Warnings** heading. For the heading **Other information**, the type size is correctly listed as 7 point. However, **Warnings** is listed as a subheading with a 6-point type size. Subheadings, such as “Do not use”, “When using this product”, and “Stop use and ask a doctor if” can be in 6-point type size, but headings in the modified format must be at least 7 points.

*Reviewer’s comment: The sponsor has clarified that the Warnings heading is 7-point type size and this is acceptable.*

3. **4 fl. oz. size Active ingredient heading** - Only the first letter should be capitalized in the heading **Active ingredient** (see 21 CFR 201.66(d)(1)).

*Reviewer’s comment: This has been corrected in the revised labeling.*

4. **For the 16 fl. oz. size using a nozzle applicator Use-** The *Use* statement is missing the letter “b” in the word “by”.

*Reviewer’s comment: This correction has been made in the 16 fl. oz. size nozzle labeling and is acceptable.*

5. **1, 4, 8, and 16 fl. oz. sizes using a nozzle applicator Directions** - The **Directions** statement (“Flush the affected eye...”) should be followed by a period to follow the directions under 21 CFR 349.78(d)(2).

*Reviewer’s comment: This correction has been made to all sizes with nozzle labeling and is acceptable.*

6. **All SKUs Use** - The *Uses* heading should be changed to *Use* since a change was made from multiple indications to a single indication.

*Reviewer’s comment: This correction has been made to the labeling for all sizes and is acceptable.*

7. **All SKUs Warnings**

- Subheadings, such as “Do not use”, “When using this product”, and “Stop use and ask a doctor if” should not be italicized.
- Periods should be placed at the end of the sentences, “Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center.” It is only necessary to bold the first statement (i.e. “Keep out of reach of children.”).

*Reviewer’s comment: These corrections have been made to the labeling for all sizes and are acceptable.*

### **III. RECOMMENDATIONS**

Issue an **APPROVAL** letter to the sponsor for the submitted Pur-Wash ophthalmic solution immediate container labels (1-, 4-, 8-, 16-[nozzle and eyecup configurations], and 32-fl. oz. sizes). Request that the sponsor submit final printed labeling (FPL) identical to the labels submitted on August 29, 2011, when available.

**IV. SUBMITTED LABELING**

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ELAINE E ABRAHAM  
08/30/2011

DEBBIE L LUMPKINS  
08/30/2011

505(b)(2) ASSESSMENT

Application Information		
NDA # 022305	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Pur-Wash Established/Proper Name: purified water Dosage Form: Solution Strengths: 98.3%		
Applicant: Niagara Pharmaceuticals Inc.		
Date of Receipt: November 1, 2010		
PDUFA Goal Date: September 1, 2011	Action Goal Date (if different):	
Proposed Indication(s): Flush eyes of foreign objects		

**GENERAL INFORMATION**

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES  NO

*If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*



**INFORMATION PROVIDED VIA RELIANCE  
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Final Monograph - 21 CFR Part 349 – Ophthalmic drug Products for Over-The-Counter Human Use, Subpart B – Active Ingredients, Sec. 349.20 Eyewashes	Complete findings of clinical effectiveness

\*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The sponsor contends that the attributes of the proposed drug product does not deviate from the Ophthalmic Drug Products for Over-the-Counter Human Use monograph (21 CFR 349) addressing eyewash products other than the fact that there is no preservative in the solution and sterility is achieved by (b) (4). The basis for the submission of this NDA is because of the sterilization by (b) (4) as stated in 21 CFR 310 (b) (4) Certain Drugs Accorded New Drug Status Through Rulemaking Procedures.

**RELIANCE ON PUBLISHED LITERATURE**

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES  NO

*If “NO,” proceed to question #5.*

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES  NO

*If “NO,” proceed to question #5.*

*If “YES”, list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?  
YES  NO



**RELIANCE ON LISTED DRUG(S)**

*Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.*

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES  NO

*If "NO," proceed to question #10.*

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)

*Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A  YES  NO

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".*

*If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES  NO

If "YES", please list which drug(s) and answer question d) i. below.  
If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES  NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

*The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.*

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES  NO

If "NO" to (a) proceed to question #11.  
If "YES" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES  NO

If “**YES**” to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If “**NO**” or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES  NO

If “**NO**”, proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES  NO

If “**YES**” and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If “**NO**” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): The following are sterile water products marketed by Braun, Baxter, and Hospira and are indicated for irrigation: NDA 16734, ANDA 17428, ANDA 17866, ANDA 18313, ANDA 17513.

**PATENT CERTIFICATION/STATEMENTS**

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed  *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES  NO

*If "NO", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the*

*NDA holder/patent owner, proceed to question #15.*

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES  NO

*If "NO", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES  NO

*If "NO", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

**Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES  NO  Patent owner(s) consent(s) to an immediate effective date of approval

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/s/  
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PHONG D DO  
08/15/2011

MELISSA H FURNESS  
08/23/2011

# 2nd Addendum Labeling Review for Pur-Wash Eyewash Ophthalmic Solution

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**SUBMISSION DATES:** August 22, 2011

**NDA/SUBMISSION TYPE:** N22-305

**ACTIVE INGREDIENTS:** Purified water USP 98.3%

**DOSAGE FORM:** Ophthalmic solution

**SPONSOR:** Niagara Pharmaceuticals, Inc. (NPI)  
60 Innovation Dr.  
Flamborough, Ontario L9H 7P3  
Canada

Robert Schiff (agent)  
Schiff & Company  
(973) 227-1830

**REVIEWER:** Elaine Abraham

**TEAM LEADER:**

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## I. BACKGROUND

Labeling recommendations for Pur-wash Eyewash (98.3% purified water) ophthalmic solution were emailed to the sponsor on August 18, 2011. Revised labeling was submitted on August 22, 2011.

<b>Submitted Labeling</b>	<b>Representative of Following SKUs</b>
1 fl. oz. (30 mL) bottle	N/A
4 fl. oz. (118 mL) bottle	N/A
8 fl. oz. (236 mL) bottle	N/A
16 fl. oz. (473 mL) bottle ( horizontal layout)	N/A
16 fl. oz. (473 mL) bottle ( vertical layout)	N/A
32 fl. oz. (946 mL) bottle	N/A

## II. REVIEWER'S COMMENTS

### A. Sponsor's response to August 18, 2011 comments

The sponsor was provided with the following labeling comments:

1. You have provided no evidence to support your assertion that consumers of your proposed OTC product understand the meaning of the word “ (b) (4) ”. This term should be removed from labeling.

**Sponsor's response: The term “ (b) (4) ” has been removed from the labeling on all sizes.**

*Reviewer's comment: This is acceptable.*

2. 21 CFR 201.61(c) requires that the statement of identity be in a size reasonably related to the most prominent printed material on the Principal Display Panel (PDP). On the current versions of the PDPs for the 1-, 4-, 8- and 16- fl oz containers there continue to be statements that are more prominent than the required statement of identity, i.e., sterile ( (b) (4) ) solution and the net contents statements. These statements distract from the required statement of identity and the prominence of these statements needs to be reduced. Alternatively, the prominence of the statement of identity can be increased by increasing the font size of the statement.

**Sponsor's response: The font size of the statement of identity is increased to display its prominence on the PDP for 1-, 4-, 8- and 16- fl oz containers. Also revised the label so that the font size on other items (mentioned above) is consistently smaller so that the difference in prominence is evident on the PDP.**

*Reviewer's comment: The PDP is acceptable based on these changes.*

3. All of the currently proposed labels appear to be using the modified format provided for in 21 CFR 201.66 (d)(10) that allows bulleted statements to continue onto the next horizontal line of text and does not require the vertical alignment of bullets. However, the use of this format requires the required labeling take up more than 60 percent of the total available surface area available to bear labeling. You will need to provide a justification for the use of the modified format for your proposed labels. Alternatively, you can revise your labels to comply with 21 CFR 201.66(d)(4) that requires that if more than one bulleted statement is placed on the same horizontal line, the end of one bulleted statement shall be separated from the beginning of the second bullet by at least two square “ems” and the complete additional bulleted statement cannot continue to the next line of text. This section also requires that additional bulleted statements appearing on each

subsequent horizontal line of text under a heading or subheading shall be vertically aligned with the bulleted statements on the previous line.

**Sponsor's response: The proposed labels for 4-, 8-, 16- and 32-fl oz containers are revised to comply with 21 CFR 201.66(d)(4).**

**Justification for Modified Format in 1-fl oz containers**

**As per 201.66 (d) (10) If title, headings, subheadings and information other than information required to appear in PDP requires more than 60% of total surface area available to bear labeling then modified format can be used. In the proposed 1- oz fl oz container the total surface area available to bear labeling has been used 100% (inclusive of PDP and Drug Facts). In the case of proposed 1- oz fl oz container the square inch %'s of the Drug Facts boxes vs. the total label is 73% and hence the modified format provided for in 21 CFR 201.66(d) (10) is used. For the 1 oz fl oz container the modified format provided for in 21 CFR 201.66 (d)(10) is used that allows bulleted statements to continue onto the next horizontal line of text and does not require the vertical alignment of bullets.**

*Reviewer's comment: The revisions based on this recommendation are acceptable. The justification for following the modified format under 21 CFR 201.66(d)(10) for the 1 fl. oz. SKU is acceptable.*

4. 21 CFR 201.66(c)(5) requires the warning "For external use only" to immediately follow the Warnings heading. Revise your proposed 1-fl oz label to comply with this provision of 210.66. In addition, this warning should not be followed by a period. Remove the period that follows this warning in all your proposed labels.

**Sponsor's response: On the 1-fl oz label to comply with the provision of 210.66(c)(5) the warning "For external use only" is revised to immediately follow the Warnings heading. Also the period that follows this warning in all proposed labels has been removed.**

*Reviewer's comment: For the 1 fl. oz. size, "For external use only" cannot be placed on the same line as the **Warnings** heading and should be moved to the next line [see 201.66(d)(6)]. The "Do not use" subheading should be moved to the line below the **Warnings** heading and "For external use only" statement so that "Do not use" is associated with the bulleted statements that follow. Using the modified format, the bulleted statement, "if you experience any open wounds..." can follow on the same line. A hairline should precede the "Do not use" subheading. The phrase "For external use only" should be in the same type size as used for the text in the label and*

*should be bolded, but not italicized so as not to diminish the prominence of the **Warnings** heading.*

5. Your proposed revised use statement for the labeling on the 4-, 8-, 16-, and 32-fl oz container labels is acceptable. However, because of the brevity of the new use statement and to increase consumer comprehension of the statement we recommend that you remove the bullets from the statement and revise it to read as follows: “For cleansing the eye to help relieve irritation or burning by removing loose foreign material”.

**Sponsor’s response: The statement for the labeling on the 4-, 8-, 16-, and 32-fl container labels is revised to read “For cleansing the eye to help relieve irritation or burning by removing loose foreign material”.**

*Reviewer’s comment: This revision to Drug Facts is acceptable.*

B. Additional recommendations:

1. Annotated specifications for Drug Facts: For the 1 fl. oz. SKU, the type size of the **Warnings** should be clarified. For the heading **Other information**, the size is correctly listed as 7 point. However, the heading **Warnings** is listed by the sponsor as a subheading with a 6-point type size. Subheadings, such as “Do not use”, “When using this product”, and “Stop use and ask a doctor if” should be in 6-point type size.
2. For the 4 fl. oz. Drug Facts label, only the first letter should be capitalized in the heading **Active ingredient** (see 21 CFR 201.66(d)(1)).
3. For the 16-fl. oz. size using a nozzle applicator, the **Use** statement is missing the letter “b” in the word “by”.
4. For all SKUs, the **Uses** heading should be changed to **Use** since the sponsor made a change from multiple indications to one indication.
5. For the 1-, 4-, 8-, and 16-fl. oz. sizes using a nozzle applicator, the **Directions** statement should be followed by a period to follow the directions under 21 CFR 349.78(d)(2).
6. Subheadings, such as “Do not use”, “When using this product”, and “Stop use and ask a doctor if” should not be italicized.
7. Under **Warnings**, for all SKUs, periods should be placed at the end of the sentences, “Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center.” It is only necessary to bold the first statement (i.e. “Keep out of reach of children.”).

### III. RECOMMENDATIONS

The labeling deficiencies listed below should be communicated to the sponsor. Labeling should be revised and resubmitted for our review. These comments all relate to the Drug Facts label and are based on 21 CFR 201.66.

1. **1 fl. oz. size Warnings** - “For external use only” cannot be placed on the same line as the **Warnings** heading and should be moved to the next line [see 21 CFR 201.66(d)(6)]. This is true even when using the modified format under 21 CFR 201.66(d)(10). The “Do not use” subheading should be moved to the line below the **Warnings** heading and “For external use only” statement so that “Do not use” is associated with the bulleted statements that follow. The bulleted statement, “if you experience any open wounds...” can follow on the same line. A hairline should precede the “Do not use” subheading. The phrase “For external use only” should be in the same type size as used for the text in the label and should be bolded, but not italicized, so as not to diminish the prominence of the **Warnings** heading.

The format below should be followed:

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**Warnings**

**For external use only**

---

**Do not use** ■ if you experience any open wounds...

2. **1 fl. oz. size annotated specifications for Drug Facts** - Clarify the type size for the **Warnings** heading. For the heading **Other information**, the type size is correctly listed as 7 point. However, **Warnings** is listed as a subheading with a 6-point type size. Subheadings, such as “Do not use”, “When using this product”, and “Stop use and ask a doctor if” can be in 6-point type size, but headings in the modified format must be at least 7 points.
3. **4 fl. oz. size Active ingredient heading** - Only the first letter should be capitalized in the heading **Active ingredient** (see 21 CFR 201.66(d)(1)).
4. **For the 16 fl. oz. size using a nozzle applicator Use-** The **Use** statement is missing the letter “b” in the word “by”.
5. **1, 4, 8, and 16 fl. oz. sizes using a nozzle applicator Directions** - The **Directions** statement (“Flush the affected eye...”) should be followed by a period to follow the directions under 21 CFR 349.78(d)(2).

6. **All SKUs Use** - The *Uses* heading should be changed to *Use* since a change was made from multiple indications to a single indication.

7. **All SKUs Warnings**

- Subheadings, such as “Do not use”, “When using this product”, and “Stop use and ask a doctor if” should not be italicized.
- Periods should be placed at the end of the sentences, “Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center.” It is only necessary to bold the first statement (i.e. “Keep out of reach of children.”).

**IV. SUBMITTED LABELING**

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

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

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/s/  
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ELAINE E ABRAHAM  
08/25/2011

DEBBIE L LUMPKINS  
08/25/2011

# Addendum Labeling Review for Pur-Wash Eyewash Ophthalmic Solution

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**SUBMISSION DATES:** May 31, 2011

**NDA/SUBMISSION TYPE:** N22-305

**ACTIVE INGREDIENTS:** Purified water USP 98.3%

**DOSAGE FORM:** Ophthalmic solution

**SPONSOR:** Niagara Pharmaceuticals, Inc. (NPI)  
60 Innovation Dr.  
Flamborough, Ontario L9H 7P3  
Canada

Robert Schiff (agent)  
Schiff & Company  
(973) 227-1830

**REVIEWER:** Elaine Abraham

**TEAM LEADER:**

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## I. BACKGROUND

The initial labeling review dated May 7, 2011 made general recommendations for (b) (4) Eyewash (98.3% purified water) ophthalmic solution, and requested revised labeling based on the monograph requirements and the guidelines for Drug Facts. Revised labeling, which included the new trade name, Pur-wash, was submitted on May 31, 2011.

Submitted Labeling	Representative of Following SKUs
1 fl. oz. (30 mL) bottle	N/A
4 fl. oz. (118 mL) bottle	N/A
8 fl. oz. (236 mL) bottle	N/A
16 fl. oz. (473 mL) bottle ( horizontal layout)	N/A
16 fl. oz. (473 mL) bottle ( vertical layout)	N/A
32 fl. oz. (946 mL) bottle	N/A

II. REVIEWER'S COMMENTS

A. Bottle labels

i. Bottle Label Outside Drug Facts

a. Trade name

The proposed trade name, Pur-Wash, has been found acceptable by DMEPA on June 21, 2011.

b. Established name and Statement of identity

1) The sponsor has revised the established name and statement of identity on the principal display panel (PDP) to:

Pur-Wash  
Eyewash  
98.3% Purified Water  
Sterile [ (b)(4) ] Solution  
Ophthalmic

The statement of identity should be revised in accordance with 21 CFR 201.61(b), which states that the statement of identity “shall be in terms of the established name of the drug... followed by an accurate statement of the general pharmacological category(ies)”. The pharmacological category should be listed according to 21 CFR 349.78(a). To follow the required format for trade name and statement of identity, the sponsor should revise this part of the PDP to:

Pur-Wash  
Purified Water, 98.3%  
Ophthalmic solution  
Eyewash

Or

Pur-Wash  
Purified Water, ophthalmic solution, 98.3%  
Eyewash

- 2) The revised established name/statement of identity should be prominent on the PDP (see 21 CFR 201.61(c)). As presently labeled, the “Single Use” and net quantity of content statements are more prominent.
- 3) The word “Sterile” is not part of the statement of identity and should be removed. The recommendation at the team labeling meeting was that “Sterile” could be moved as part of the “Single Use” statement to read “Sterile for Single Use Only” or to another location on the PDP. However, as the

sterilization of the product is still pending a final microbiology review, this is not included in the recommendations to the sponsor.

- 4) The word “<sup>(b)(4)</sup>” should be removed from the label as it has no meaning to the consumer.

**c. “Single Use” statement**

DMEPA recommends additional language on the PDP to clarify the meaning of single use by revising the statement “Single Use” to “Single Use Only, Discard Any Unused Solution After One Use”. This is to increase comprehension among consumers that the bottle needs to be discarded after one use. Although this would be acceptable, there is no regulatory requirement that it be placed on the PDP. As the Drug Facts already includes the statements “[bullet] do not reuse [bullet] once opened, discard” under the **When using this product** section, we are not recommending that this statement be added to the PDP.

**d. Questions**

1. For the **4, 8, 16, and 32 fl. oz. bottles** - The contact information for the sponsor listed on the PDP (“Questions ? [telephone pictogram] Call 905 690-62779 a.m. to 5 p.m. EST Mon-Fri”) should be moved to Drug Facts under “**Questions?**” (see 21 CFR 201.66(c)(9)).
2. For the **1 fl. oz. bottle** - This SKU does not contain a Questions number on the PDP or elsewhere. It is not clear if the manufacturer’s phone number on the PDP can be used to report problems, but if it can, the number should be under the **Questions** section. Unless the packaging includes a toll-free number through which consumers can report complaints to the manufacturer, the Drug Facts label must contain a statement including FDA’s toll-free MedWatch telephone number as specified in 21 CFR 201.66(c)(5)(vii). (See A. iii. Drug Facts Label - 1 fl. oz. bottle below.)

**e. Net quantity of contents**

We recommend that the standard abbreviation for milliliter(s), “mL”, be used in place of ml.

**ii. Drug Facts Label - All SKUs**

- a. Headings** - Only the first letter should be capitalized in the headings, “**Other information**” and “**Inactive ingredients**” (see 21 CFR 201.66(d)(1)). The headings are not followed by punctuation (see 21 CFR 201.66(c)). The colons following the headings, “**When using this product**”, “**Stop use and ask a doctor if**”, and “**Directions**” should be removed. Also, only the actual subheading language (“**Stop use and ask a doctor if**”) as listed in 21 CFR 201.66(c)(5)(vii) should be bolded. Text following the subheading should be unbolded.
- b. Format** - The first letter of text following bullets should not be capitalized (see Drug Facts format examples).
- c. Active ingredient** - Only the first letter should be capitalized, as in “Purified water”, to follow the Drug Facts format examples.
- d. Purpose** - The purpose should be listed according to 21 CFR 349.78(a) as “Eyewash” (no space between eye and wash).

e. **Warnings**

- 1) Keep out of reach of children - “Keep out of *the* reach of children” should be revised to “Keep out of reach of children” (see 201.66(c)(5)(x)).
- 2) In the statement, “If swallowed, get medical help or contact a Poison Control Centre right away”, “Centre” should be spelled as commonly used in the U.S., “Center”.
- 3) Section 21 CFR 201.66(c) requires that warnings in (c)(5) appear in the order listed. The warning “Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away” should be moved to the end of the **Warnings** section and placed before the **Directions** section. These warnings should be separated from the rest of the warnings by a hair line (see 21 CFR 201.66(d)(8)).
- 4) The sponsor was requested to either remove the statement (b) (4) or provide their rationale for this age cutoff. This statement has been removed from the **Warnings** section which is acceptable.
- 5) In the **Warnings** section under the **Do not use** subheading, for better consumer understanding, we recommend that the statement “■ if you experience any open wounds in or near the eyes and obtain immediate medical treatment” be revised to “[bullet] if you have any open wounds in or near the eyes, and get medical help right away”.
- 6) For better flow of language and consumer understanding, we recommend revising the warning “Stop use and ask a doctor if you experience: ■ eye pain ■ changes in vision ■ continued redness ■ irritation of the eye ■ condition worsens or persists” to “**Stop use and ask a doctor if** you have any of the following [bullet] eye pain [bullet] changes in vision [bullet] continued redness or irritation of the eye [bullet] condition worsens or persists”. Only the actual subheading language (“**Stop use and ask a doctor if**”) as listed in 21 CFR 201.66(c)(5)(vii) should be bolded as stated above.

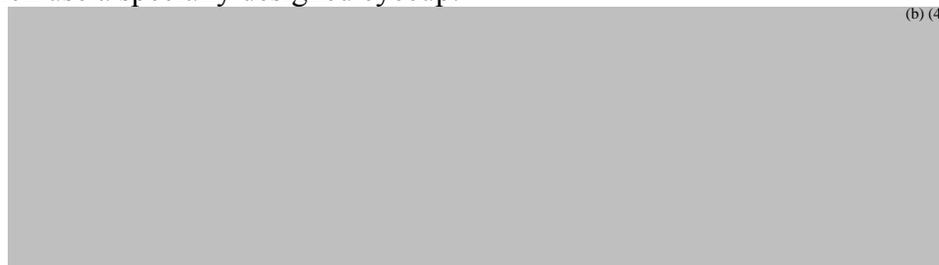
f. **Directions**

1) **Nozzle (1, 4, 8, and 16 fl. oz.)**

The directions follow the monograph directions under 21 CFR 349.78(d)(2) and are acceptable.

2) **Eyecup (16 and 32 fl. oz.)**

The sponsor has proposed the following directions for the larger size bottles which use a specially designed eyecup:



These directions generally follow the directions under 21 CFR 349.78(d)(1) with some changes as relate to the modified eyecup. The hyphen should be removed from the first use of the word “eyecup” so that it follows the spelling of the word in 21 CFR 349.78(d)(1). Also the comma following the word “bottle” in the last sentence should be removed to follow the monograph. The directions are acceptable with these changes, however, bulleted statements should be used for directions for easier reading (see 21 CFR 201.66(c)(6)) as in the following:

- [bullet] remove tamper evident seal and cap
- [bullet] replace with sterile eyecup provided
- [bullet] avoid contamination of rim and inside surfaces of the eyecup
- [bullet] place eyecup surface to the affected eye, pressing tightly to prevent the escape of the liquid and tilt the head backward
- [bullet] open eyelids wide and rotate eyeball while controlling the rate of flow of solution by pressure on the bottle to ensure thorough bathing with the wash

Note: The second and third use of the word “sterile” prior to the word eyecup has been removed but this is not required.

**g. Other information**

- 1) Tamper evident feature** - The sponsor was requested to revise the tamper-evident statement on the label to include an identifying characteristic (e.g., a pattern, name, registered trademark, logo, or picture) in accordance with 21 CFR 211.132, and the identifying characteristic should be included in the tamper-evident feature. In the “*Other information*” section, the sponsor has revised the statement “Do not use if seal (b)(4) is broken or missing” to “For your protection, this bottle has an imprinted white seal with black printing “TAMPER EVIDENT SEAL”. ■ Do not use if this seal is missing or broken”.

A [bullet] should precede the statement beginning with “for your protection...” (see 21 CFR 201.66(d)(4)).

- 2) Storage conditions** - The chemistry review recommended that the product be labeled for storage under USP controlled room temperature (20 to 25°C, or 68 to 77°F) because the proposed post-approval stability study did not include intermediate storage conditions (b)(4). The chemist’s recommendation was to revise the storage condition information on the label to “product for storage under USP controlled room temperature (20° to 25°C (68° to 77°F))”. Because the average consumer is not familiar with the USP reference or language such as “USP controlled room temperature”, we recommend that under *Other information*, the statement “Store at room temperature (b)(4)” be changed to “[bullet] store at 20° to 25°C (68° to 77°F)”.

**h. Inactive ingredients** - lower case should be used for all ingredients. Also, the period at the end of the inactive ingredient list should be removed (see Drug Facts format examples).

**i. Font Specifications**

Font specifications have been provided and the labels meet the requirements listed in 21 CFR 201.66(d).

**iii. Drug Facts Label - 1 fl. oz. bottle**

- a. The label follows the modified Drug Facts format under 21 CFR 201.66(d)(10) and is acceptable.
- b. **Uses** - The following revisions should be made based on 21 CFR 349.78(b)(1).
  - 1) Add the word “loose” before “foreign material”.
  - 2) Add a space between (b) (4)
  - 3) Remove the period at the end of the statement (see Drug Facts format examples).
- c. The 1 fl. oz. bottle does not include a Questions contact phone number. Unless the packaging includes a toll-free number through which consumers can report complaints to the manufacturer, the Drug Facts label must contain a statement including FDA’s toll-free MedWatch telephone number (see 21 CFR 201.66(c)(5)(vii)). If a Questions contact number is not included, the following text should immediately follow the subheading **Stop use and ask a doctor if:** “[Bullet] side effects occur. You may report side effects to FDA at 1-800-FDA-1088.”

**iv. Drug Facts Label - 4 fl. oz. bottle**

Only the first letter should be capitalized in the heading, “**Active ingredient**” (see 21 CFR 201.66(d)(1)).

**v. Drug Facts Label - 4, 8, 16, and 32 fl. oz. bottle**

- a. **Uses** - (b) (4) should be preceded by a [bullet] and the word “or” removed from the line. If space is limited, it is not necessary to list all of the indication choices included under 21 CFR 349.78(b)(2) in the monograph under the **Uses** section, although consistency between labels should be considered (see 21 CFR 201.66(d)(4) and 349.78(b)(2)).
- b. **Questions?** - We recommend that the sponsor include a “**Questions?**” section, and move the telephone number and the days of the week and times of the day when a person is available to respond to questions from the PDP to this section (see 21 CFR 201.66(c)(9)).

**B. Lot number and expiration date**

The sponsor was requested to make provisions for the lot or control number and the expiration date. The sponsor stated that “The lot number (21 CFR 201.18) and the expiration date (21 CFR 201.17 and 211.137(d)) are applied to each bottle using an ink

jet printer. The location of lot number and expiration date is now included in the “*Other information*” section of the Drug Facts panel.” This is acceptable.

### C. Tamper evident feature on bottle

The seal on the bottle contains a mix of English (b) (4) (TAMPER EVIDENT SEAL (b) (4)). The sponsor should remove the (b) (4) as only English language should be used on the tamper-evident seal for products marketed in the U.S. in accordance with 21 CFR 201.15 (c)(1).

## III. RECOMMENDATIONS

The labeling deficiencies listed below should be communicated to the sponsor. Labeling should be revised and resubmitted for our review.

### A. Principal Display Panel (PDP) - All SKUs

- 1) Established name/Statement of Identity - The statement of identity should be revised in accordance with 21 CFR 201.61(b), which states that the statement of identity “shall be in terms of the established name of the drug... followed by an accurate statement of the general pharmacological category(ies)”. The pharmacological category should be listed according to 21 CFR 349.78(a). The following format should be used:

Trade name  
Established name, dosage form, dosage strength  
Pharmacological category

Or

Trade name  
Established name, dosage strength  
Dosage form  
Pharmacological category

To follow the required format for trade name, established name and statement of identity, either of the following would be acceptable:

Pur-Wash  
Purified Water, 98.3%  
Ophthalmic solution  
Eyewash

Or

Pur-Wash  
Purified Water, ophthalmic solution, 98.3%  
Eyewash

- The revised established name/statement of identity should be prominent on the PDP (see 21 CFR 201.61(c)). As the PDP is presently designed, other statements appear more prominent than the established name/statement of identity, including the “Single Use” statement and the net quantity of contents.
  - The word “Sterile” is not part of the statement of identity and should be removed.
  - The word “(b) (4)” is not part of the statement of identity and should be removed from the PDP as it has no meaning to the consumer.
- 2) The Questions and contact information should be moved from the PDP to Drug Facts (see B. Drug Facts Label - 4, 8, 16, and 32 fl. oz. bottles below).

#### B. Drug Facts Label - All SKUs

- 1) Headings - Only the first letter should be capitalized in the headings, “***Other information***” and “***Inactive ingredients***” (see 21 CFR 201.66(d)(1)). The headings are not followed by punctuation (see 21 CFR 201.66(c)). Remove the colons following the headings, “**When using this product**”, “**Stop use and ask a doctor if**,” and “**Directions**”. Also, only the actual subheading language (“**Stop use and ask a doctor if**”) as listed in 21 CFR 201.66(c)(5)(vii) should be bolded. Text following the subheading should be unbolded.
- 2) Format - The first letter of text following bullets should not be capitalized (see Drug Facts format examples under 21 CFR 201.66).
- 3) **Active ingredient** - Only the first letter be capitalized, as in “Purified water” (see Drug Facts format examples under 21 CFR 201.66).
- 4) **Purpose** - The purpose should be listed according to 21 CFR 349.78(a) as “Eyewash” (no space between eye and wash).
- 5) **Warnings**
  - a) Keep out of reach of children - “Keep out of *the* reach of children” should be revised to “Keep out of reach of children” (see 201.66(c)(5)(x)).
  - b) In the statement, “If swallowed, get medical help or contact a Poison Control Centre right away”, “Centre” should be spelled as commonly used in the U.S., “Center”.
  - c) Section 21 CFR 201.66(c) requires that the warnings in (c)(5) appear in the order listed. The warning “Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.” should be moved to the end of the **Warnings** section and placed before the **Directions** section. These warnings should be separated from the rest of the warnings by a hair line (see 21 CFR 201.66(d)(8)).

6) **Other information**

- a) Tamper evident statement - A bullet should precede the statement beginning with “for your protection, this bottle has been imprinted...” (see 21 CFR 201.66(d)(4)).
  - b) Storage conditions - Under **Other information**, the statement “Store at room temperature [redacted] (b)(4)” should be revised to “[bullet] store at 20° to 25°C (68° to 77°F)”. These storage conditions are based on the USP definition of “controlled room temperature” and are supported by submitted stability data.
- 7) Under **Inactive ingredients**, lower case should be used for all ingredients. The period at the end of the inactive ingredient list should be removed (see Drug Facts format examples under 21 CFR 201.66).

**C. Drug Facts Label - 1 fl. oz. bottle**

- 1) **Uses** - The following revisions should be made based on 21 CFR 349.78(b)(1).
  - a) Add the word “loose” before “foreign material”.
  - b) Add a space between [redacted] (b)(4)
  - c) Remove the period at the end of the statement (see Drug Facts format examples under 21 CFR 201.66).
- 2) The 1 fl. oz. bottle, unlike the other bottle sizes, does not include a Questions contact phone number. Unless the packaging includes a toll-free number through which consumers can report complaints to the manufacturer, the Drug Facts label must contain a statement including FDA’s toll-free MedWatch telephone number (see 21 CFR 201.66(c)(5)(vii)). If a Questions contact number is not included, the following text should immediately follow the subheading **Stop use and ask a doctor if**: “[Bullet] side effects occur. You may report side effects to FDA at 1-800-FDA-1088.”

**D. Drug Facts Label - 4 fl. oz. bottle**

Only the first letter should be capitalized in the heading, “**Active ingredient**” (see 21 CFR 201.66(d)(1)).

**E. Drug Facts Label - 4, 8, 16, and 32 fl. oz. bottles**

- 1) Under **Uses**, revise “[bullet] [redacted] (b)(4) with a [bullet] and removing the word “or” from the line. If space is limited, it is not necessary to list all of the indication choices included in 21 CFR 349.78(b)(2) under the **Uses** section, although consistency between labels should be considered (see 21 CFR 201.66(d)(4) and 349.78(b)(2)).
- 2) The contact information listed on the PDP (“Questions? [telephone pictogram] Call 905 690-62779 a.m. to 5 p.m. EST Mon-Fri”) should be moved to Drug Facts under “**Questions?**” (see 21 CFR 201.66(c)(9)).

**F. Drug Facts - 16 and 32 fl. oz. eyecup directions**

**Directions** - The hyphen should be removed from the first use of the word “eyecup” so that it follows the spelling of the word in 21 CFR 349.78(d)(1). Also remove the

comma following the word “bottle” in the last sentence to follow the monograph. Revising the format to include bulleted statements should be used for directions for easier reading (see 21 CFR 201.66(c)(6)) as in the following:

- [bullet] remove tamper evident seal and cap
- [bullet] replace with sterile eyecup provided
- [bullet] avoid contamination of rim and inside surfaces of the eyecup
- [bullet] place eyecup surface to the affected eye, pressing tightly to prevent the escape of the liquid and tilt the head backward
- [bullet] open eyelids wide and rotate eyeball while controlling the rate of flow of solution by pressure on the bottle to ensure thorough bathing with the wash

Note: The second and third use of the word “sterile” prior to the word eyecup has been removed but this is not required.

#### G. Tamper evident feature on bottle

The seal on the bottle contains a mix of English (b) (4) (TAMPER EVIDENT SEAL and (b) (4)). Remove the (b) (4) as only English language should be used on the tamper-evident seal for products marketed in the U.S. in accordance with 21 CFR 201.15 (c)(1).

The following items are not required but are labeling recommendations that should be communicated to the sponsor:

#### A. PDP - All SKUs

Net quantity of contents - We recommend that the standard abbreviation for milliliter(s), “mL”, be used in place of ml to state the net quantity of contents.

#### B. Drug Facts - All SKUs

- 1) In the **Warnings** section under the **Do not use** subheading, for better consumer understanding, we recommend that the statement “■ if you experience any open wounds in or near the eyes and obtain immediate medical treatment” be revised to “[bullet] if you have any open wounds in or near the eyes, and get medical help right away”.
- 2) In the **Warnings** section under the **Stop use and ask a doctor if** subheading, for better flow of language, we recommend revising the warning “Stop use and ask a doctor if you experience: ■ eye pain ■ changes in vision ■ continued redness ■ irritation of the eye ■ condition worsens or persists” to “**Stop use and ask a doctor if** you *have any of the following* [bullet] eye pain [bullet] changes in vision [bullet] continued redness or irritation of the eye [bullet] condition worsens or persists” (italics added for emphasis). Note: Bolding the subheading “**Stop use and ask a doctor if**” is required but the rest of the warning should be unbolded (see above).

**IV. SUBMITTED LABELING**

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ELAINE E ABRAHAM  
07/29/2011

DEBBIE L LUMPKINS  
07/29/2011

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medication Error Prevention and Risk Management**

Date: June 20, 2011

Application Type/Number: NDA 022305

To: Andrea Leonard-Segal, M.D., M.S., Director  
Division of Nonprescription Clinical Evaluation

Through: Zachary Oleszczuk, Pharm.D., Team Leader  
Carol Holquist, R.Ph., Director  
Division of Medication Error Prevention and Analysis

From: Yelena Maslov, Pharm.D., Safety Evaluator  
Division of Medication Error Prevention and Analysis

Subject: Proprietary Name, Label, and Labeling Review

Drug Name(s): Pur-Wash (Purified Water) Ophthalmic Solution, 98.3%

Applicant/sponsor: Niagara Pharmaceuticals, Inc

OSE RCM #: 2011-523 and 2011-782

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

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## **EXECUTIVE SUMMARY**

This review summarizes DMEPA's evaluation of the proposed proprietary name as well as labels and labeling for Pur-Wash (Purified Water) Ophthalmic Solution. The proposed product characteristics for the product are provided in Appendix B. Our evaluation did not identify concerns that would render the name unacceptable based on product characteristics and safety profile known at the time of this review. Thus, DMEPA finds the proposed proprietary name, Pur-Wash, acceptable for this product.

DMEPA considers this a final review; however, if approval of the NDA is delayed beyond 90 days from the date of this review, The Division of Nonprescription Clinical Evaluation should notify DMEPA because the proprietary name must be re-reviewed prior to the new approval date. Additionally, if any of the proposed product characteristics as stated in this review are altered, DMEPA rescinds this finding and the name must re-submitted for review. The conclusions upon re-review are subject to change.

Additionally, our evaluation of the container labels, drug facts labeling, and packaging for this product noted the areas of needed improvement in order to minimize the potential for medication errors. We provided our recommendations regarding the labels and labeling in Section 5.

## **1 BACKGROUND**

### **1.1 INTRODUCTION**

This review responds to a request from Niagara Pharmaceuticals, Inc., dated May 11, 2011, for a safety and promotional assessment of the proposed proprietary name, Pur-Wash (NDA 022305).

### **1.2 REGULATORY HISTORY**

Pur-Wash is the second proposed proprietary name for this product. The first proposed proprietary name, (b) (4) was withdrawn by the Applicant on April 26, 2011, because DMEPA informed the Applicant via teleconference held on the same date that we identified two other international products by the name (b) (4). However, those products contain different active ingredients.

## **2 METHODS AND MATERIALS**

Appendix A describes the general methods and materials used by the Division of Medication Error Prevention and Analysis (DMEPA) when conducting a proprietary name risk assessment for all proprietary names. Sections 2.1, 2.2, and 2.3 identify specific information associated with the methodology for reviewing the proposed proprietary name, Pur-Wash. Additionally, Section 2.4 identifies specific methodology and materials we use to evaluate the label and labeling.

## 2.1 SEARCH CRITERIA

For this review, a particular consideration was given to drug names beginning with the letter 'P' when searching to identify potentially similar drug names, as 75% of the confused drug names reported by the USP-ISMP Medication Error Reporting Program involve pairs beginning with the same letter.<sup>1,2</sup>

To identify drug names that may look similar to Pur-Wash, the DMEPA safety evaluators also consider the orthographic appearance of the name on the lined and unlined orders. Specific attributes are taken into consideration include the length of the name (seven letters and one dash), upstrokes (three, Capital 'P', capital 'W', and lower case letters 'h' or two if 'w' is scripted in a lower case), down strokes (none), cross strokes (none), and dotted letters (none). Additionally, several letters in the proposed name, Pur-Wash, may be vulnerable to ambiguity when scripted (See Appendix C). As such, the DMEPA staff also considers these alternate appearances when identifying drug names that may look similar to Pur-Wash.

When searching to identify potential names that may sound similar to Pur-Wash, DMEPA safety evaluators search for the names with the similar number of syllables (two, pur-wash), stresses (Pur-wash or pur-WASH), and placement of vowel and consonant sounds. Additionally, DMEPA safety evaluators consider that pronunciation of part of the name can vary (See Appendix C). The Applicant's intended pronunciation [pyoor-wosh] was also taken into consideration, as it was included in the Proprietary Name review Request. Moreover, names are often mispronounced or spoken with regional accents and dialects, so other pronunciations of the names are considered.

## 2.2 FDA PRESCRIPTION ANALYSIS STUDIES

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, the following inpatient and verbal orders were communicated during FDA prescription studies conducted on May 23, 2011.

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<sup>1</sup> Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at <http://www.ismp.org/Tools/confuseddrugnames.pdf>

<sup>2</sup> Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artificial Intelligence in Medicine (2005)

**Figure 1. Pur-Wash Study (Conducted on 05/23/2011)**

Handwritten Requisition Medication Order	Verbal Prescription
<p><u>Medication Order:</u></p> <p><i>Pur-wash Apply to eyes as directed</i></p>	<p>Pur-Wash #4 oz</p> <p>Use as directed</p>
<p><u>Outpatient Prescription:</u></p> <p><i>Pur-wash</i></p> <p><i>UD</i></p> <p><i>#4 oz</i></p>	

### 2.3 FDA ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE SEARCH

Since there are other Purified Water Ophthalmic Solutions currently marketed, DMEPA searched for medication errors involving Purified Water Ophthalmic Solutions to identify potential errors that may occur with Pur-Wash.

The AERS search conducted on May 20, 2011 used the following search terms: MedDRA High Level Group Terms (HLGT) “Medication Errors” and “Product Quality Issues” along with active ingredient name “Purified%” and verbatim “Purified%” and “Ocuire%”.

### 2.4 LABELS, LABELING, AND PACKAGING RISK ASSESSMENT

We use Failure Mode and Effects Analysis<sup>3</sup> (FMEA), the principles of human factors, and lessons learned from the post marking experience to identify potential sources of error with the proposed product labels and insert labeling. Thereafter, we provide recommendations that aim at reducing the risk of medication errors. For Pur-Wash, the Applicant submitted the following container labels on May 31, 2011 (see Appendix G for the container label images):

- Container Labels: 1 Fl Oz (30 mL), 4 Fl Oz (118 mL), 8 Fl Oz (236 mL), 16 Fl Oz (473 mL), 32 Fl Oz (946 mL)

## 3 RESULTS

The following sections describe the findings of database and information sources searches, FDA prescription studies, expert panel discussions, AERS searches, and labels and labeling evaluations.

<sup>3</sup> Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

### **3.1 DATABASE AND INFORMATION SOURCES**

The DMEPA safety evaluators' searches yielded a total of ten names (n=10) as having some similarity to the proposed proprietary name, Pur-Wash.

Nine (n=9) of the ten names were thought to look like Pur-Wash by the safety evaluators. These names are Puri-Clens, BP Wash, Panscol, Procort, Prometh, Duramist Plus, Eye Wash, Periochip, and Duravent.

The remaining name (n=1), Peri-Wash, was thought to look and sound like Pur-Wash.

### **3.2 EXPERT PANEL DISCUSSION**

The Expert Panel reviewed the pool of names identified by DMEPA safety evaluators (See Section 3.1 above) and noted no additional names thought to have orthographic or phonetic similarity to the name Mylafem.

DDMAC had no concerns regarding the proposed name from a promotional perspective and did not offer any additional comments relating to the proposed names.

DMEPA noted that DDMAC found this name acceptable, but found a similar proposed name, Pure-Sleep\*\*\*, unacceptable from a promotional standpoint. On June 15, 2011, DMEPA sent an email to DDMAC asking for clarification on the different decision on these names. DDMAC responded on June 16, 2011 stating "We did not object to Pur-wash because it is purified water indicated to flush the eyes of foreign objects. We did not feel that this name was misleading."

### **3.3 FDA PRESCRIPTION ANALYSIS STUDIES**

A total 41 practitioners responded to the FDA Prescription Analysis studies. None of the responses overlapped with a currently marketed product. Thirteen participants interpreted the proposed proprietary name correctly as 'Pur-Wash' or 'Pur Wash' with correct interpretations occurring with inpatient orders (n=4), and outpatient orders (n=9). The remaining twenty-eight participants misinterpreted the name, Pur-Wash. The most common interpretation occurred with thirteen participants misinterpreting the dash '-' in Pur-Wash as the letter 'e'. See Appendix D for the complete listing of interpretations from the verbal and written prescription studies.

### **3.4 FDA ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE**

Zero reports involving Purified Water Ophthalmic Solution were identified in the Adverse Event Reporting System (AERS) database.

### **3.5 COMMENTS FROM THE DIVISION OF NONPRESCRIPTION CLINICAL EVALUATION**

#### ***3.5.1 Initial Phase of Review***

In response to OSE email on May 31, 2011, the Division of Nonprescription Clinical Evaluation (DNCE), Division of Nonprescription Regulation Development (DNRD), and Division of Transplant and Ophthalmology Products (DTOP) indicated that they do not have any concerns with the proprietary name. However, one reviewer stated that 'PUR' is a trade name for a line of water filtering products. Additionally, the reviewer expressed a concern regarding potential confusion between Pur-Wash with "PUR" product line for water filtering products due to name similarity.

DMEPA notes that “PUR” product line for water filtering products is not related to medicine and does not represent a medical product. Thus, the confusion between Pur-Wash and “PUR” is unlikely to occur.

### **3.5.2 Midpoint of Review**

DMEPA notified DNCE, DNRD, and DTOP via email June 2, 2011 that we find the name Pur-Wash acceptable. DNCE, DNRD, and DTOP did not have any additional comments.

### **3.4 SAFETY EVALUATOR SEARCH**

The primary safety evaluator identified twelve additional names (n=12), which were thought to look or sound similar to Pur-Wash and represent a potential source of drug name confusion.

Ten names (n=10) were thought to look like Pur-Wash by the primary safety evaluator. These names are Purinethol, Parnate, Percocet, Primovist, Demadex, Prevacid, Duranest, Duricef, Durahist, and Durezol.

The remaining two names (n=2), Pure Wash and Bio Pure Eye Wash, were thought to look and sound like Pur-Wash by the primary safety evaluator.

### **3.5 LABELS, LABELING, AND PACKAGING RISK ASSESSMENT**

Our evaluation of the proposed container labels, drug facts labeling, and product packaging identified the following deficiencies:

- The statement of identify is not presented in the recommended manner and should be revised.
- The word ‘Eyewash’ appears directly under the proprietary name and may be misinterpreted as a part of the proprietary name.
- The manufacturer’s information appears on the principle display panel and competes with the prominence of other important information.
- The net quantity appears more prominent than the statement of identify and more be misinterpreted as the strength of the product.
- The principle display panel of the label does not state that the product should be discarded after one use.
- The heading ‘Questions’ and information associated with this heading appears on the principle display panel and competes with the prominence of other important information.
- The two largest container bottles (i.e., 16 Fl Oz and 32 Fl Oz) are proposing to use eyewash sterile cups instead of nozzle.

## **4 DISCUSSION**

The proprietary name, Pur-Wash, was evaluated from a safety and promotional perspectives based on the product characteristics provided by the Applicant.

#### **4.1 PROMOTIONAL ASSESSMENT**

DDMAC did not find the name, Pur-Wash, promotional. DNCE, DNRD, DTOP, and DMEPA concurred with this assessment.

#### **4.2 SAFETY ASSESSMENT OF THE PROPRIETARY NAME**

The safety assessment considered the orthographic and phonetic similarity of the proposed proprietary name to the currently marketed drugs, the results of the prescription studies, and other aspects of the name that might be a source of confusion. A total of twenty-two names (n=23) were identified for the potential similarity to the proposed name, Pur-Wash (10 names from the database searches, 12 names from the independent safety evaluator searches, and 1 name from DNCE). We determined that all twenty-three names will not pose a risk of confusion as described in Appendices E and F.

#### **4.3 LABELS, LABELING, AND PACKAGING RISK ASSESSMENT**

Pur-Wash should be used only once and discarded after one use because it does not contain preservatives. As a result, appropriate labeling is important to emphasize that the product is for single use only on the principle display panel to ensure consumers are aware not to re-use the product. This is particularly important for larger bottle sizes of 16 Fluid ounces (473 mL) and 32 Fluid ounces (946 mL), because the consumers may continue re-using the product and thus, may introduce the risk of infection.

The container labels contain the word ‘ (b) (4) as a part of the dosage form. This word does not carry any significance for healthcare practitioners or consumers and does not make sense. Thus, the use of the word ‘ (b) (4) as a part of the dosage form on the principle display panel is unacceptable.

Additionally, product’s tamper-evident seal is written in two languages, English and (b) (4). However, per 21 CFR 201.15 (c)(1), all words, statements, and other information that appears on labels and labeling should be stated in English language unless the product is distributed solely in the Commonwealth of Puerto Rico or in a Territory where the predominant language is one other than English. Thus, we believe the tamper-evident seal should be written in English language only.

### **5 CONCLUSIONS AND RECOMMENDATIONS**

DMEPA concludes the proposed proprietary name is acceptable from both a promotional and safety perspective. However, if any of the proposed product characteristics as stated in this review are altered, DMEPA rescinds this finding and the name must be resubmitted for review. The conclusions upon re-review are subject to change. We will notify the Applicant of this finding via letter.

The proposed proprietary name, Pur-Wash, must be re-reviewed if NDA approval is delayed beyond 90 days.

The labels and labeling can be improved to be more consistent with other over-the-counter products and clarify that this product is for single use only. See comments in Section 5.1 for our recommendations for the labels and labeling.

## 5.1 COMMENTS TO THE APPLICANT

### A. Container Label 1 oz, 4 oz, 8 oz, 16 oz, and 32 oz

1. Relocate the word “Eyewash” to appear beneath the statement of identity. As currently presented, “Eyewash” appears to be a part of the proprietary name. However, it should appear in the statement of identity as a pharmacological category of the product.
2. In an effort to make the labels and labeling for over-the-counter products more consistent, we recommend revising the statement of identify in a following format:

Established name, dosage form, dosage strength  
Pharmacological category

Thus, the proprietary name and statement of identify should appear in the following manner:

Pur-Wash  
Purified Water, ophthalmic solution, 98.3%  
Eyewash

3. Delete the word “(b) (4)” from the dosage form as this word does not carry any significance to healthcare professionals or consumers and may be confusing.
4. Decrease the prominence of the manufacturer’s information on the principle display panel by decreasing the font size of the information. As currently presented, the manufacturer’s information occupies space and competes for prominence with other important information on the principle display panel.
5. Relocate the heading “Questions” and information associated with this heading from the principle display panel to the Drug Facts underneath the Section “Inactive Ingredients” as illustrated in 21 CFR 201.66. As currently presented on the principle display panel, this information occupies space and competes for prominence with other important information on the principle display panel such as statement of identity.
6. Increase the prominence of the statement of identity on the principle display panel as this important information appears less prominent than the net quantity and thus, may be overlooked.
7. Decrease the prominence of the net quantity on the principle display panel. As currently presented, the net quantity (e.g., 1 Fl Oz [30 ml]) is more prominent than the statement of identify and may be misinterpreted as a strength of the product.
8. Revise the statement “Single Use” to explicitly state “Single Use Only, Discard Any Unused Solution After One Use” to increase comprehension among consumers that the bottle needs to be discarded after one use.
9. Revise the abbreviation for milliliters (i.e., ‘ml’) to appear in a lower case letter ‘m’ and a capital letter ‘L’ (i.e., ‘mL’).
10. Use only English language on the tamper-evident seal in accordance with 21 CFR 201.15 (c)(1).

## 6 REFERENCES

1. ***Micromedex Integrated Index*** (<http://csi.micromedex.com>)

Micromedex contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

2. ***Phonetic and Orthographic Computer Analysis (POCA)***

POCA is a database which was created for the Division of Medication Error Prevention and Analysis, FDA. As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion.

3. ***Drug Facts and Comparisons, online version, St. Louis, MO***  
(<http://factsandcomparisons.com> )

Drug Facts and Comparisons is a compendium organized by therapeutic course; it contains monographs on prescription and OTC drugs, with charts comparing similar products.

4. ***FDA Document Archiving, Reporting & Regulatory Tracking System [DARRTS]***

DARRTS is a government database used to organize Applicant and Sponsor submissions as well as to store and organize assignments, reviews, and communications from the review divisions.

5. ***Division of Medication Errors Prevention and Analysis proprietary name consultation requests***

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

6. ***Drugs@FDA*** (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>)

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official

information about FDA approved brand name, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and “Chemical Type 6” approvals.

**7. *Electronic online version of the FDA Orange Book***  
(<http://www.fda.gov/cder/ob/default.htm>)

The FDA Orange Book provides a compilation of approved drug products with therapeutic equivalence evaluations.

**8. *U.S. Patent and Trademark Office*** (<http://www.uspto.gov>)

USPTO provides information regarding patent and trademarks.

**9. *Clinical Pharmacology Online*** ([www.clinicalpharmacology-ip.com](http://www.clinicalpharmacology-ip.com))

Clinical Pharmacology contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. It also provides a keyword search engine.

**10. *Data provided by Thomson & Thomson’s SAEGIS™ Online Service, available at***  
([www.thomson-thomson.com](http://www.thomson-thomson.com))

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and trade names that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

**11. *Natural Medicines Comprehensive Databases*** ([www.naturaldatabase.com](http://www.naturaldatabase.com))

Natural Medicines contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

**12. *Access Medicine Database*** (<http://www.accessmedicine.com/drugs.aspx>)

Access Medicine contains full-text information from approximately 60 medical titles: it includes tables and references. Among the database titles are: Goodman and Gilman’s The Pharmacological Basis of Therapeutics, Current Medical Diagnosis and Treatment, Tintinalli’s Emergency Medicine, and Hurst’s the Heart.

**13. *USAN Stems*** (<http://www.ama-assn.org/ama/pub/about-ama/our-people/coalitions-consortiums/united-states-adopted-names-council/naming-guidelines/approved-stems.shtml>)

USAN Stems List contains all the recognized USAN stems.

**14. *Red Book Pharmacy’s Fundamental Reference***

Red Book contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

**15. Lexi-Comp ([www.lexi.com](http://www.lexi.com))**

Lexi-Comp is a web-based searchable version of the Drug Information Handbook.

**16. Medical Abbreviations Book**

Medical Abbreviations Book contains commonly used medical abbreviations and their definitions.

**17. LabelDataPlus Database (<http://www.labeldataplus.com/index.php?ns=1>)**

LabelDataPlus database covers a total of 36773 drug labels. This includes Human prescription drug labels as well as Active Pharmaceutical Ingredients (APIs), OTC (Application and Monograph) drugs, Homeopathic drugs, Unapproved drugs, and Veterinary drugs.

## **APPENDICES**

### **Appendix A**

FDA's Proprietary Name Risk Assessment considers the promotional and safety aspects of a proposed proprietary name. The promotional review of the proposed name is conducted by DDMAC. DDMAC evaluates proposed proprietary names to determine if they are overly fanciful, so as to misleadingly imply unique effectiveness or composition, as well as to assess whether they contribute to overstatement of product efficacy, minimization of risk, broadening of product indications, or making of unsubstantiated superiority claims. DDMAC provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.

The safety assessment is conducted by DMEPA. DMEPA staff search a standard set of databases and information sources to identify names that are similar in pronunciation, spelling, and orthographically similar when scripted to the proposed proprietary name. Additionally, we consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.). DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.<sup>4</sup>

Following the preliminary screening of the proposed proprietary name, DMEPA gathers to discuss their professional opinions on the safety of the proposed proprietary name. This meeting is commonly referred to the Center for Drug Evaluation and Research (CDER) Expert Panel discussion. DMEPA also considers other aspects of the name that may be misleading from a safety perspective. DMEPA staff conducts a prescription simulation studies using FDA health care professionals. When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

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<sup>4</sup> National Coordinating Council for Medication Error Reporting and Prevention.  
<http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name and misleading nature of the proposed proprietary name with a focus on the avoidance of medication errors.

DMEPA uses the clinical expertise of its staff to anticipate the conditions of the clinical setting where the product is likely to be used based on the characteristics of the proposed product. DMEPA considers the product characteristics associated with the proposed product throughout the risk assessment because the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed proprietary name include, but are not limited to; established name of the proposed product, proposed indication of use, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. DMEPA considers how these product characteristics may or may not be present in communicating a product name throughout the medication use system. Because drug name confusion can occur at any point in the medication use process, DMEPA considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.<sup>5</sup> The product characteristics considered for this review appears in Appendix B1 of this review.

The DMEPA considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA compares the proposed proprietary name with the proprietary and established name of existing and proposed drug products and names currently under review at the FDA. DMEPA compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names because verbal communication of medication names is common in clinical settings. DMEPA examines the phonetic similarity using patterns of speech. If provided, DMEPA will consider the Sponsor's intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Sponsor has little control over how the name will be spoken in clinical practice. The orthographic appearance of the proposed name is evaluated using a number of different handwriting samples. DMEPA applies expertise gained from root-cause analysis of postmarketing medication errors to identify sources of ambiguity within the name that could be introduced when scripting (e.g., "T" may look like "F," lower case 'a' looks like a lower case 'u,' etc). Additionally, other orthographic attributes that determine the overall appearance of the drug name when scripted (see Table 1 below for details).

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<sup>5</sup> Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

**Table 1.** Criteria Used to Identify Drug Names that Look- or Sound-Similar to a Proposed Proprietary Name.

<b>Type of Similarity</b>	<b>Considerations when Searching the Databases</b>		
	<i>Potential Causes of Drug Name Similarity</i>	<i>Attributes Examined to Identify Similar Drug Names</i>	<i>Potential Effects</i>
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	<ul style="list-style-type: none"> <li>Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication</li> <li>Names may look similar when scripted and lead to drug name confusion in written communication</li> </ul>
	Orthographic similarity	Similar spelling Length of the name/Similar shape Upstrokes Down strokes Cross-strokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	<ul style="list-style-type: none"> <li>Names may look similar when scripted, and lead to drug name confusion in written communication</li> </ul>
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	<ul style="list-style-type: none"> <li>Names may sound similar when pronounced and lead to drug name confusion in verbal communication</li> </ul>

Lastly, DMEPA considers the potential for the proposed proprietary name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. Consequently, DMEPA considers and evaluates these broader safety implications of the name throughout this assessment and the medication error staff provides additional comments related to the

safety of the proposed proprietary name or product based on professional experience with medication errors.

### **1. Database and Information Sources**

DMEPA searches the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to the proposed proprietary name. A standard description of the databases used in the searches is provided in the reference section of this review. To complement the process, the DMEPA uses a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, DMEPA reviews the USAN stem list to determine if any USAN stems are present within the proprietary name. The individual findings of multiple safety evaluators are pooled and presented to the CDER Expert Panel. DMEPA also evaluates if there are characteristics included in the composition that may render the name unacceptable from a safety perspective (abbreviation, dosing interval, etc.).

### **2. Expert Panel Discussion**

DMEPA gathers CDER professional opinions on the safety of the proposed product and discussed the proposed proprietary name (Expert Panel Discussion). The Expert Panel is composed of Division of Medication Errors Prevention (DMEPA) staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC). We also consider input from other review disciplines (OND, ONDQA/OBP). The Expert Panel also discusses potential concerns regarding drug marketing and promotion related to the proposed names.

The primary Safety Evaluator presents the pooled results of the database and information searches to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend additional names, additional searches by the primary Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

### **3. FDA Prescription Simulation Studies**

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically

scanned and one prescription is delivered to a random sample of participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants record their interpretations of the orders which are recorded electronically.

#### **4. Comments from Other Review Disciplines**

DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with DDMAC's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to provide any further information that might inform DMEPA's final decision on the proposed name.

Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

#### **5. Safety Evaluator Risk Assessment of the Proposed Proprietary Name**

The primary Safety Evaluator applies his/her individual expertise gained from evaluating medication errors reported to FDA, considers all aspects of the name that may be misleading or confusing, conducts a Failure Mode and Effects Analysis, and provides an overall decision on acceptability dependent on their risk assessment of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.<sup>6</sup> When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed proprietary name to be confused with another drug name because of name confusion and, thereby, cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to orthographically or phonetically similar drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the primary Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is has not been marketed, the primary Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product

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<sup>6</sup> Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

characteristics listed in Appendix B1 of this review. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, Expert Panel Discussion, and prescription studies, external studies, and identifies potential failure modes by asking:

***“Is the proposed proprietary name convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting? And Are there any components of the name that may function as a source of error beyond sound/look-alike”***

An affirmative answer indicates a failure mode and represents a potential for the proposed proprietary name to be confused with another proprietary or established drug name because of look- or sound-alike similarity or because of some other component of the name. If the answer to the question is no, the Safety Evaluator is not convinced that the names possess similarity that would cause confusion at any point in the medication use system, thus the name is eliminated from further review.

In the second stage of the Risk Assessment, the primary Safety Evaluator evaluates all potential failure modes to determine the likely *effect* of the drug name confusion, by asking:

***“Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?”***

The answer to this question is a central component of the Safety Evaluator’s overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would not ultimately be a source of medication errors in the usual practice setting, the primary Safety Evaluator eliminates the name from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend the use of an alternate proprietary name.

Moreover, DMEPA will object to the use of proposed proprietary name when the primary Safety Evaluator identifies one or more of the following conditions in the Overall Risk Assessment:

- a. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the Review Division concurs with DDMAC’s findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a PROPRIETARY name or otherwise [21 U.S.C 321(n); See also 21 U.S.C. 352(a) & (n)].
- b. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].

- c. FMEA identifies the potential for confusion between the proposed proprietary name and other proprietary or established drug name(s), and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
- d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.
- e. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, the proprietary name may be misleading or, inadvertently, introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product but involve a naming characteristic that when incorporated into a proprietary name, may be confusing, misleading, cause or contribute to medication errors.

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the primary Safety Evaluator uses the FMEA process to identify strategies to reduce the risk of medication errors. DMEPA generally recommends that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name. In that instance, DMEPA may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, DMEPA will provide a contingency objection based on the date of approval. Whichever product, the Agency approves first has the right to use the proprietary name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

The threshold set for objection to the proposed proprietary name may seem low to the Applicant/Sponsor. However, the safety concerns set forth in criteria a through e above are supported either by FDA regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), the Joint Commission, and the Institute for Safe Medication Practices (ISMP). These organizations have examined medication errors resulting from look- or sound-alike drug names, confusing, or misleading names and called for regulatory authorities to address the issue prior to approval. Additionally, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and preventable source of medication error that, in many instances, the Agency and/or Sponsor can identify and rectify prior to approval to avoid patient harm.

Furthermore, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to rectify post-approval. Educational and other post-approval efforts are low-leverage strategies that have had limited effectiveness at alleviating medication errors involving drug name confusion. Sponsors have undertaken higher-leverage strategies, such as drug name changes, in the

past but at great financial cost to the Sponsor and at the expense of the public welfare, not to mention the Agency’s credibility as the authority responsible for approving the error-prone proprietary name. Moreover, even after Sponsors’ have changed a product’s proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioners’ vocabulary, and as a result, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, DMEPA believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval.

**Appendix B:** Product Characteristics Provided for Pur-Wash

**Pur-Wash**  
(Purified Water)  
NDA# 022305  
/pyoor-wosh/

**Indication:** For cleaning the eye to help relieve irritation, (b) (4) burning, (b) (4) (b) (4) by removing loose foreign material, (b) (4)

**Route:** Ophthalmic

**Dosage Form:** Solution

**Strength:** 98.3%

**Dose:** Flush the affected eye as needed, controlling the rate of flow of solution by pressure on the bottle

**How supplied:** 30 mL (1 Fl oz), 118 mL (4 Fl oz), 236 mL (8 Fl oz), 473 mL (16 Fl oz), 946 mL (32 Fl oz)

**Applicant:** Niagara Pharmaceuticals, Inc.

**Appendix C:** Letters with Possible Orthographic or Phonetic Misinterpretation

Letters in Name, Pur-Wash	Scripted May Appear as	Spoken May Be Interpreted as
Capital ‘P’	‘B’, ‘D’, ‘N’, ‘R’	‘B’
lower case ‘p’	‘g’, ‘j’	‘b’
lower case ‘u’	‘n’, ‘v’, ‘w’	any vowel
lower case ‘r’	n, s, or v	‘w’
lower case ‘w’	‘a’, ‘eu’, ‘m’, ‘an’, ‘ne’, ‘en’	‘l’
lower case ‘a’	‘re’, ‘ce’, ‘o’, ‘u’, ‘n’	Any vowel
lower case ‘s’	‘v’, ‘r’, ‘c’	‘x’
Lower case ‘h’	‘b’, ‘n’, ‘l’	

**Appendix D:** Prescription Simulation Samples and Results

**Figure 1. Pur-Wash Study (Conducted on 05/23/2011)**

<b>Handwritten Requisition Medication Order</b>	<b>Verbal Prescription</b>
<u>Medication Order:</u> <i>Pur-Wash Apply to eyes as directed</i>	Pur-Wash #4 oz Use as directed
<u>Outpatient Prescription:</u> <i>Pur-Wash UD #4 oz</i>	

**FDA Prescription Simulation Responses.**

<b>Inpatient Medication Order</b>	<b>Outpatient Prescription</b>	<b>Voice Prescription</b>
Parbrush	Pan Wash	Pure Wash
Pur Wash	Pur Wash	Pure Wash
Pur-Wash	Pur-Wash	Pure Wash
Pur-Wash	Pur-Wash	Pure Wash
Pur-Wash	Pur-Wash	Pure Wash
PurBash	Pur-Wash	Pure Wash
PurBrash	Pur-Wash	PureWash
PurBrash	Pur-Wash	PureWash
PurBrash	Pur-Wash	PureWash
PurBrush	Pur-Wash	PureWash
PurBrush	Pure Wash	PureWash
PurBrush	Pure Wash	
Purlrash	PurWash	
Purlrash		
Purlrash		
Purlrash		
Purtrash		

**Appendix E:** Proprietary names not likely to be confused or not used in usual practice settings for the reasons described.

Product Name	Similarity to Pur-Wash	Failure preventions
BP Wash (Benzoyl Peroxide)	Look alike	Lacks sufficient orthographic similarity
Primovist <sup>***</sup> (Gadoxetate Disodium)	Look alike	This proprietary name for NDA (b) (4) was found unacceptable by DDMAC due to promotional concerns. The NDA was approved on 07/03/2008 under proprietary name, Eovist.
Eye Wash (Purified Water)	Look alike	This name is only found in DARRTS database as the product name for NDA 022305. However, the proposed proprietary name for the product is Pur-Wash, which is the subject of this review.
Duranest MPF and Epinephrine (Etidocaine and Epinephrine)	Looks alike	Discontinued without generic equivalent.
Puri-Clens	Look alike	No information available from any of the databases commonly used databases listed in Reference Section.
Pure Wash	Look alike and sound alike	This trademark is only found in Thomson and Thomson Saegis Database, but not in any other commonly used databases listed in Reference Section. This is not a name of the product, but it is a trademark for multiple soaps, detergents, natural perfumes, and cosmetics in Japan.
Pure Wash (antibacterial skin cleanser)	Look and sound alike	Abandoned trademark. This name is only found in United States Patent and Trademark Office database, but not in any other commonly used databases listed in Reference Section. The trademark was filed on 04/28/1994 and abandoned on 03/31/2005.
Bio Pure Eye Wash (Purified water)	Look alike and sound alike	Abandoned trademark. This name is only found in United States Patent and Trademark Office database, but not in any other commonly used databases listed in Reference Section. The trademark was filed on 02/04/2006 and abandoned on 10/04/2006.
Peri-Wash	Looks and sounds alike	This name is not a product name, but a common name for multiple perineal washes used in cleaning of urine, emesis, and fecal matter and odor elimination from the soiled skin (e.g., No Rinse Peri Wash, Coloplast Peri-Wash II, Bedside-Care Perineal Wash, Sween Peri Wash, etc.)
PUR	Looks alike and sounds alike	Trade name for water filter system and not a medical product or related to medicine.

\*\*\* This document contains proprietary and confidential information that should not be released to public

**Appendix F:** Risk of medication errors due to product confusion minimized by dissimilarity of the names and/ or use in clinical practice for the reasons described.

<b>Proposed name: Pur Wash (Purified Water) Ophthalmic Solution</b>	<b>Strength(s): 98.3%</b>	<b>Usual dose: Flush the affected eye as needed, controlling the rate of flow of solution by pressure on the bottle.</b>
<b>Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion</b>	<b>Causes (could be multiple)</b>	<b>Prevention of Failure Mode</b>
Purinethol (Mercaptopurine) Tablets, 50 mg  <u>Usual Dose</u> 2.5 mg/kg/day to 5 mg/kg/day orally once daily or 80 mg/m <sup>2</sup> /day to 100 mg/m <sup>2</sup> /day orally once daily. Maintenance dosages are 1.5 mg/kg/day to 2.5 mg/kg/day PO once daily	<u>Orthographic</u> Both letters share the letter string ‘Pur-’. Additionally, the letter ‘w’ in Pur-Wash may appear similar to the letter string ‘-in-’ in Purinethol when scripted.  <u>Strength</u> Both products are single strength products, thus, the strength may be omitted.	<u>Orthographic</u> The name Pur-Wash contains 3 upstrokes whereas the name Purinethol contains 4 upstrokes. Additionally, the letter string ‘-ash’ in Pur-Wash lacks orthographic similarity with the letter string ‘-ethol’ in Purinethol when scripted.  <u>Usual Dose</u> Flush the affected eye(s) as needed vs. 1 tablet to 2 tablets.
Parnate (Tranlycypromine Sulfate) Tablets, 10 mg  <u>Usual Dose</u> 30 mg to 60 mg orally in divided doses.	<u>Orthographic</u> Both names start with the letter ‘P’. Additionally, the letter string ‘-ur-wa-’ in Pur-Wash may appear similar to the letter string ‘-arna-’ in Parnate when scripted if the letter ‘w’ is scripted in a lower case.  <u>Strength</u> Both products are single strength products, thus, the strength may be omitted.	<u>Orthographic</u> The name Pur-Wash appears longer than the name Parnate due to the wider letter ‘w’ in the middle of the name. The last upstroke letters in both names appear in different positions. Additionally, the letter string ‘-sh’ in Pur-Wash lacks orthographic similarity to the letter string ‘-te’ in Parnate when scripted.  <u>Usual Dose</u> Flush the affected eye(s) vs. 1 tablet  <u>Frequency of Administration</u> As needed vs. two to three times daily.

<p>Percocet (Oxycodone and Acetaminophen) Tablets, 2.5 mg/325 mg, 5 mg/325 mg, 7.3 mg/325 mg, 7.5 mg/500 mg, 10 mg/325 mg, 10 mg/650 mg</p> <p><u>Usual Dose</u> 2.5 mg/325 mg to 10 mg/650 mg orally every 6 hours as needed for pain.</p>	<p><u>Orthographic</u> Both names start with the letter 'P'. Additionally, both names contain two upstrokes in the same positions, if the letter 'w' is scripted in a lower case. Additionally, the letter string '-ur-wa-' in 'Pur-wash' may appear similar to the letter string '-ercoce-' in Percocet when scripted.</p>	<p><u>Strength</u> 98.3% vs. 2.5 mg/325 mg, 5 mg/325 mg, 7.3 mg/325 mg, 7.5 mg/500 mg, 10 mg/325 mg, 10 mg/650 mg</p> <p><u>Usual Dose</u> Flush the affected eye(s) vs. 1 tablet</p> <p><u>Frequency of Administration</u> As needed vs. every 6 hours as needed for pain</p>
<p>Demadex* (Torsemide) Tablets,  5mg, 10 mg, 20 mg, 100 mg Injection: 10 mg/mL</p> <p><u>Usual Dose</u> 5 mg to 200 mg orally once daily depending on the indication. * Proprietary name, Demadex Injection, is discontinued, however, multiple generic products are available.</p>	<p><u>Orthographic</u> The letter string 'Pur-wa-' in 'Pur-Wash' may appear similar to the letter string 'Dema-' in Demadex when scripted if the letter 'w' is scripted in a lower case.</p> <p><u>Strength</u> Both products are single strength products, thus, the strength may be omitted (Injection).</p>	<p><u>Orthographic</u> The letter string 'sh' in Pur-Wash lacks orthographic similarity to the letter string '-dex' in Demadex when scripted.</p> <p><u>Usual Dose</u> Flush the affected eye(s) vs. 1 tablet</p> <p><u>Route of Administration</u> Ophthalmic vs. Intravenous (Injection)</p>

<p>Prevacid (Lansoprazole) Delayed-release Capsules: 15 mg and 30 mg</p> <p>Orally Disintegrating Tablets: 15 mg and 30 mg</p> <p>Delayed-release Granules for Suspension: 15 mg and 30 mg</p> <p>Powder for Injection: 30 mg</p> <p><u>Usual Dose</u> Oral: 15 mg to 30 mg orally once daily Intravenous: 30 mg intravenously over 30 minute infusion for up to 7 days.</p>	<p><u>Orthographic</u> Both names share the first letter ‘P’. Additionally, the letter string ‘ur-wa’ may appear similar to the letter string ‘-revaci-’ in Prevacid when scripted if the letter ‘w’ is scripted in a lower case.</p> <p><u>Strength</u> Both products are single strength products, thus, the strength may be omitted (Powder for Injection).</p>	<p><u>Orthographic</u> The name Pur-Wash appears longer than the name Prevacid when scripted due to wider letters ‘u’ and ‘w’.</p> <p><u>Dosage Form</u> Ophthalmic Solution vs. Delayed-release Capsule, Tablet, Delayed-release Granules for Suspension, or Powder for Injection; thus, the dosage form has to be specified on a prescription for Prevacid.</p> <p><u>Usual Dose</u> Flush the affected eye(s) vs. 1 tablet or 1 capsule</p> <p><u>Route of Administration</u> Ophthalmic vs. Intravenous (Injection)</p>
<p>Duricef (Cefadroxil) Capsule, 500 mg</p> <p>Tablet, 1000 mg</p> <p>Powder for Oral Suspension: 125 mg/5 mL, 250 mg/5 mL, 500 mg/5 mL</p> <p><u>Usual Dose</u> Children and adolescents: 30 mg/kg/day in two divided doses. Adults: 1 g to 2 g orally in one to two divided doses</p>	<p><u>Orthographic</u> The letter string ‘Pur-w-’ in Pour-Wash may appear similar to the letter string ‘Duric-’ in Duricef when scripted, if the letter ‘w’ in scripted in a lower case.</p> <p><u>Strength</u> Both products are single strength products, thus, the strength may be omitted (Capsules or Tablets).</p>	<p><u>Orthographic</u> The name Duricef contains a down stroke letter ‘f’ vs. the name Pur-Wash does not. Additionally, the name Pur-Wash appears longer than the name Duricef when scripted due to wider letters ‘w’ and ‘a’ in the middle of the name Pur-Wash.</p> <p><u>Usual Dose</u> Flush the affected eye(s) vs. 1 tablet to 2 tablets or 1 teaspoonful to 2 teaspoonfuls</p> <p><u>Dosage Form</u> Ophthalmic Solution vs. Capsule, tablet, or Powder for Suspension</p> <p><u>Frequency of Administration</u> As needed vs. twice daily</p>

<p>Durezol (Difluprednate) Ophthalmic Solution, 0.05%</p> <p><u>Usual Dose</u> Instill 1 drop into the conjunctival sac of the affected eye(s) four times daily beginning 24 hours after surgery for two weeks, then decrease to twice daily for one week.</p>	<p><u>Orthographic</u> The letter string ‘Pur-’ may appear similar to the letter string ‘Dur’ when scripted.</p> <p><u>Dosage Form</u> Both products are ophthalmic solutions</p> <p><u>Strength</u> Both products are single strength products, thus, the strength may be omitted.</p>	<p><u>Orthographic</u> The letter string ‘-wash’ lacks orthographic similarity to the letter string ‘-ezol’ when scripted, even if the letter ‘w’ is scripted in a lower case. Additionally, the name Pur-Wash appears longer than the name Durezol when scripted due to the wider letter ‘w’.</p> <p><u>Frequency of Administration</u> As needed vs. four times a day or twice daily</p>
<p>Panscol (Salicylic Acid) Ointment, 3%</p> <p><u>Usual Dose</u> Apply to affected area for wart removal.</p>	<p><u>Orthographic</u> Both names share the first letter ‘P’. Additionally, the letter string ‘-ur-’ in Pur-Wash may appear similar to the letter string ‘-an-’ in Panscol.</p> <p><u>Strength</u> Both products are single strength products, thus, the strength may be omitted.</p>	<p><u>Orthographic</u> The letter string ‘-wash’ lacks orthographic similarity to the letter string ‘-scol’ when scripted, even if the letter ‘w’ is scripted in a lower case. Additionally, the name Pur-Wash appears longer than the name Panscol when scripted due to the wider letter ‘w’.</p>
<p>Procort (Hydrocortisone) Rectal Cream, 30 mg</p> <p><u>Usual Dose</u> Apply to affected area as a thin film two to four times daily depending on the severity of symptoms</p>	<p><u>Orthographic</u> Both names start with the letter ‘P’. Additionally, the letter string ‘-ur-w-’ in the name Pur-Wash may appear similar to the letter string ‘-roco-’ in the Procort when scripted, if the letter ‘w’ is scripted in a lower case.</p> <p><u>Strength</u> Both products are single strength products, thus, the strength may be omitted.</p>	<p><u>Orthographic</u> The letter string ‘-ash’ in the name Pur-Wash lacks orthographic similarity to the letter string ‘rt’ in Procort when scripted. Additionally, the name Pur-Wash appears longer than the name Procort when scripted due to the wider letter ‘w’.</p> <p><u>Route of Administration</u> Ophthalmic vs. Rectal</p> <p><u>Frequency of Administration</u> As needed vs. every 12 hours</p>

<p>Duramist Plus (Oxymetazoline) Nasal Solution, 0.05%</p> <p><u>Usual Dose</u> One to two drops of spray to each nostril twice daily</p>	<p><u>Orthographic</u> The letter string ‘Pur-w’ may appear to the letter string ‘Dura-’ when scripted. If the letter ‘w’ is scripted in a lower case.</p> <p><u>Strength</u> Both products are single strength products, thus, the strength may be omitted.</p>	<p><u>Orthographic</u> The letter ‘-a- in Pur-Wash lacks orthographic similarity with the letter string ‘-mi- in the name Durahist when scripted. Additionally, Duramist Plus includes a modifier that helps differentiate the products.</p> <p><u>Route of Administration</u> Ophthalmic vs. Nasal</p> <p><u>Frequency of Administration</u> As needed vs. every 12 hours</p> <p><u>Usual Dose</u> Flush eyes vs. 1 spray to 2 spray</p>
<p>Periochip (Chlorhexidine gluconate) chip, 2.5 mg</p> <p><u>Usual Dose</u> Insert chip into periodontal pocket (usually done at the dentist’s office)</p>	<p><u>Orthographic</u> Both names start with the letter ‘P’. Additionally, the letter string ‘-ur-’ in Pur- Wash may appear similar to the letter string ‘-eri-’ in Periochip when scripted.</p> <p><u>Strength</u> Both products are single strength products, thus, the strength may be omitted.</p>	<p><u>Orthographic</u> The letter string ‘-wash’ in Pur-Wash lacks orthographic similarity to the letter strip ‘-ochip’ when scripted, even if the letter ‘w’ appears in a lower case.</p> <p><u>Dosage Form</u> Ophthalmic Solution vs. chip</p> <p><u>Route of Administration</u> Ophthalmic vs. periodontal</p>
<p>Durahist (Chlorpheniramine, Methscopolamine, and Pseudoephedrine) Extended- release Tablets, 2 mg/1.25 mg/10 mg</p> <p><u>Usual Dose</u> Take 1 tablet every 12 hours</p>	<p><u>Orthographic</u> The letter string ‘Pur-w’ may appear to the letter string ‘Dura-’ when scripted, if the letter ‘w’ is scripted in a lower case.</p> <p><u>Strength</u> Both products are single strength products, thus, the strength may be omitted.</p>	<p><u>Orthographic</u> The letter string ‘-ash’ in Pur-Wash lacks orthographic similarity with the letter string ‘-hist’ in the name Durahist when scripted.</p> <p><u>Usual Dose</u> Flush eyes vs. 1 tablet</p> <p><u>Frequency of Administration</u> As needed vs. every 12 hours</p>

<p>Duravent* (Chlorpheniramine, Methscopolamine, and Phenylephrine) Chewable Tablets, 8 mg/1.25 mg/60 mg</p> <p>*Proprietary name is discontinued; however, multiple generic products are available.</p> <p><u>Usual Dose</u> Take 1 tablet every 4 to 6 hours.</p>	<p><u>Orthographic</u> The letter string ‘Pur-w’ may appear to the letter string ‘Dura-’ when scripted, if the letter ‘w’ is scripted in a lower case.</p> <p><u>Strength</u> Both products are single strength products, thus, the strength may be omitted.</p>	<p><u>Orthographic</u> The letter string ‘-ash’ in Pur-Wash lacks orthographic similarity with the letter string ‘-vent’ in the name Duravent when scripted.</p> <p><u>Frequency of Administration</u> As needed vs. every 4 to 6 hours.</p> <p><u>Usual Dose</u> Flush eyes vs. 1 tablet</p>
<p>Prometh* (Promethazine) Tablet, 12.5 mg, 25 mg, 50 mg</p> <p>Oral Solution: 6.25 mg/5 mL Oral Syrup: 6. 25 mg/5 mL</p> <p>Rectal Suppository: 12.5 mg, 25 mg, 50 mg</p> <p>Injection: 25 mg/mL and 50 mg/mL</p> <p><u>Usual Dose</u> 6.25 mg to 50 mg orally, rectally, intravenously, or intramuscularly every 12 hours or every 4 to 6 hours as needed depending on indication.</p>	<p><u>Orthographic</u> Both names start with the letter ‘P’ and end with the letter ‘h’. Additionally, the letter string ‘-urw-’ appears similar to the letter string ‘-rom-’ when scripted, if the letter ‘w’ in scripted in a lower case</p>	<p><u>Orthographic</u> The letter string ‘-as-’ in Pur-Wash lacks orthographic similarity to the letter string ‘-et-’ in Prometh when scripted.</p> <p><u>Dosage Form</u> Ophthalmic Solution vs. Tablet, Oral Solution, Oral Syrup, Rectal Suppository, and Injection</p> <p><u>Strength</u> 98.3% vs. 6.25 mg, 12.5 mg, 25 mg, 50 mg</p> <p><u>Frequency of Administration</u> As needed vs. every 12 hours or 4 to 6 hours depending on the indication.</p> <p><u>Usual Dose</u> Flush eyes vs. 1 tablet</p>

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ZACHARY A OLESZCZUK on behalf of YELENA L MASLOV  
06/20/2011

ZACHARY A OLESZCZUK  
06/20/2011

CAROL A HOLQUIST  
06/21/2011

**NDA REGULATORY FILING REVIEW**  
**(Including Memo of Filing Meeting)**

NDA # 22-305 Supplement # n/a Efficacy Supplement Type SE- n/a

Proprietary Name: (b)(4) Eye Wash  
Established Name: purified water  
Strengths: (b)(4)

Applicant: Niagara Pharmaceuticals Inc.  
Agent for Applicant (if applicable): Dr. Robert Schiff, Schiff & Company

Date of Application: 30-Jan-08  
Date of Receipt: 26-Feb-08  
Date clock started after UN: n/a  
Date of Filing Meeting: 15-Apr-08  
Filing Date: 25-Apr-08  
Action Goal Date (optional): n/a User Fee Goal Date: 26-Dec-08

Indication(s) requested: Flush eyes of foreign objects

Type of Original NDA: (b)(1)  (b)(2)   
AND (if applicable)  
Type of Supplement: (b)(1)  (b)(2)

**NOTE:**

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S  P   
Resubmission after withdrawal?  Resubmission after refuse to file?   
Chemical Classification: (1,2,3 etc.) 3  
Other (orphan, OTC, etc.) OTC

Form 3397 (User Fee Cover Sheet) submitted: YES  NO

User Fee Status: Paid  Exempt (orphan, government)   
Waived (e.g., small business, public health)

**NOTE:** If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES  NO   
If yes, explain: n/a

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES  NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? n/a YES  NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES  NO   
If yes, explain: n/a
- If yes, has OC/DMPQ been notified of the submission? n/a YES  NO
- Does the submission contain an accurate comprehensive index? YES  NO   
If no, explain: Index does not reference Modules 4 or 5.
- Was form 356h included with an authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. agent must sign.**

Note: Form 356h is included, but is signed only by the foreign applicant. The U.S. agent has not signed the 356h as required.

- Submission complete as required under 21 CFR 314.50? YES  NO   
If no, explain:

1) The field copy required by 314.50 was not submitted (this should have been submitted to HQ since the manufacturer is foreign).

2) The application form, Form 356h, is signed only by the foreign applicant. The U.S. agent has not signed the 356h as required by 314.50(a)(5).

3) The index does not include reference to Modules 4 & 5 as required by 314.50(b).

4) The summary required by 314.50(c) was not submitted.

5) The field copy certification required by 314.50(d)(1)(v) was not submitted.

6) The non-clinical pharmacology and toxicology section required by 314.50(d)(2) does not include any information except a statement that the proposed product is a monographed drug and that the monograph requirements have been met. However, the eyewash monograph referenced in the cover letter cannot be referenced to support this NDA for non-clinical pharmacology and toxicology purposes because the preliminary chemistry review of this NDA indicates that there are a number of differences between the proposed (b)(4) eyewash and the (b)(4) product included in the monograph.

7) The human pharmacokinetics and bioavailability section and information supporting the sponsor's request for a waiver of bioavailability studies required by 314.50(d)(3) was not submitted.

8) The clinical section required by 314.50(d)(5) does not include any information except a statement that the proposed product is a monographed drug and that the monograph requirements have been met. However, the eyewash monograph referenced in the cover letter cannot be referenced to support this NDA for clinical purposes because the preliminary chemistry review of this NDA indicates that there are a number of differences between the proposed (b)(4) eyewash and the (b)(4) product included in the monograph.

9) The pediatric use section required by 314.50(d)(7) was not submitted.

10) The patent information (including Form 3542) required by 314.50(h) was not submitted.

11) The patent certification does not include the wording required by 314.50(i)(1)(ii).

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES
2. This application is an eNDA or combined paper + eNDA YES   
This application is: All electronic  Combined paper + eNDA   
This application is in: NDA format  CTD format   
Combined NDA and CTD formats

Does the eNDA, follow the guidance?  
(<http://www.fda.gov/cder/guidance/2353fnl.pdf>) YES  NO

**If an eNDA, all forms and certifications must be in paper and require a signature.**

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES   
**If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.**

Additional comments:

- Patent information submitted on form FDA 3542a? YES  NO
- Exclusivity requested? YES, \_\_\_\_\_ Years NO   
*NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*
- Correctly worded Debarment Certification included with authorized signature? YES  NO

Note: Debarment Certification not submitted.

**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**

*NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e.,*

“[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as “To the best of my knowledge . . .”

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?  
YES  NO   
Note: PREA is triggered by this application because it is for a new dosage form; however, PREA is not addressed in the application. Pediatric information was not submitted. Requests for deferral/waiver of pediatric studies were not submitted.
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)?  
n/a YES  NO
- Is this submission a partial or complete response to a pediatric Written Request? YES  NO   
If yes, contact PMHT in the OND-IO
- Financial Disclosure forms included with authorized signature? YES  NO   
**(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)**  
**NOTE:** Financial disclosure is required for bioequivalence studies that are the basis for approval.  
Note: Clinical and bioequivalence studies were not submitted. Only CMC studies were submitted.
- Field Copy Certification (that it is a true copy of the CMC technical section) YES  NO
- PDUFA and Action Goal dates correct in tracking system? YES  NO   
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? YES  NO   
If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: 77,883
- Are the trade, established/proper, and applicant names correct in COMIS? YES  NO   
If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) \_\_\_\_\_ NO   
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) 06-Sep-07 NO   
If yes, distribute minutes before filing meeting.
- Any SPA agreements? Date(s) \_\_\_\_\_ NO   
If yes, distribute letter and/or relevant minutes before filing meeting.

**Project Management**

- If Rx, was electronic Content of Labeling submitted in SPL format? n/a YES  NO   
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:  
Was the PI submitted in PLR format? n/a YES  NO   
If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? n/a YES  NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? n/a YES  NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? N/A  YES  NO
- Risk Management Plan consulted to OSE/IO? N/A  YES  NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA  YES  NO

**If Rx-to-OTC Switch or OTC application:**

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES  NO   
Note: Not consulted because we are refusing to file this application.
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES  NO

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? n/a YES  NO

**Chemistry**

- Did applicant request categorical exclusion for environmental assessment? YES  NO   
If no, did applicant submit a complete environmental assessment? n/a YES  NO   
If EA submitted, consulted to EA officer, OPS? n/a YES  NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES  NO   
Note: Not consulted because we are refusing to file this application.
- If a parenteral product, consulted to Microbiology Team? YES  NO   
Note: Consulted to Microbiology Team because it is a sterile product.

ATTACHMENT

**MEMO OF FILING MEETING**

DATE: 15-Apr-08

NDA #: 22-305

DRUG NAMES: (b)(4) Eye Wash (b)(4) purified water) ophthalmic solution

APPLICANT: Niagara Pharmaceuticals Inc. (Agent: Dr. Robert Schiff, Schiff & Company)

BACKGROUND: This product was marketed for several years without an NDA. The sponsor claimed the product met the monograph for eyewashes. However, this NDA is for an eyewash that is sterilized by (b)(4) Under 21 CFR 310. (b)(4) all drugs that are (b)(4), which would include this over-the-counter eyewash, require a New Drug Application. We met with the sponsor on September 6, 2007 to discuss this. The collaborative review division for this application is the Division of Anti-Infective and Ophthalmology Products.

ATTENDEES: Joel Schiffenbauer, Bindi Nikhar, Joe Porres, Marina Chang, Arlene Solbeck, Jennifer Harris, William Boyd, Wiley Chambers, Wafa Harrouk, Shulin Ding, Yubing Tang, Bryan Riley, Chuck Bonapace, Thamban Valappil, Mushfiqur Rashid, Geri Smith, Maureen Dillon Parker, Darrell Lyons, Mary Vienna.

ASSIGNED REVIEWERS (including those not present at filing meeting) :

<u>Discipline/Organization</u>	<u>Reviewer</u>
Medical:	Joe Porres
Secondary Medical:	Jennifer Harris
Statistical:	Mushfiqur Rashid
Pharmacology:	Wafa Harrouk
Statistical Pharmacology:	n/a
Chemistry:	Yubing Tang
Environmental Assessment (if needed):	n/a
Biopharmaceutical:	Chuck Bonapace
Microbiology, sterility:	Bryan Riley
Microbiology, clinical (for antimicrobial products only):	n/a
IDS:	Arlene Solbeck
DSI:	n/a
OPS:	n/a
Regulatory Project Management:	Geri Smith
Other Consults:	n/a

Per reviewers, are all parts in English or English translation? YES  NO   
If no, explain: n/a

CLINICAL FILE  REFUSE TO FILE

- Clinical site audit(s) needed? YES  NO   
If no, explain: We are refusing to file this NDA.
- Advisory Committee Meeting needed? YES, date if known n/a NO

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A  YES  NO

CLINICAL MICROBIOLOGY N/A  FILE  REFUSE TO FILE

STATISTICS N/A  FILE  REFUSE TO FILE

BIOPHARMACEUTICS FILE  REFUSE TO FILE

- Biopharm. study site audits(s) needed? n/a YES  NO

PHARMACOLOGY/TOX N/A  FILE  REFUSE TO FILE

- GLP audit needed? YES  NO

Note: Because we are refusing to file this NDA.

CHEMISTRY FILE  REFUSE TO FILE

- Establishment(s) ready for inspection? YES  NO

- Sterile product? YES  NO

If yes, was microbiology consulted for validation of sterilization?

YES  NO

**ELECTRONIC SUBMISSION:**

Any comments: n/a

**REGULATORY CONCLUSIONS/DEFICIENCIES:**

**(Refer to 21 CFR 314.101(d) for filing requirements.)**

The application is unsuitable for filing. Explain why:  
This application does not contain the minimum information required to file an application. As noted throughout this review, there are numerous regulatory/administrative, clinical, pre-clinical, and labeling deficiencies. Please refer to the individual discipline filing reviews for additional details regarding discipline-specific filing issues. In addition, there are numerous CMC issues that will be communicated to the applicant in the refuse-to-file letter.

The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

No filing issues have been identified.

Filing issues to be communicated by Day 74. List (optional):

**ACTION ITEMS:**

1.  Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2.  If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3.  If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

n/a

4.  If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

n/a

5.  Convey document filing issues/no filing issues to applicant by Day 74.  
Note: RTF issues to be communicated to applicant by Day 60.

Gerri Smith / 04-22-08  
Regulatory Project Manager

## Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

**Appendix B to NDA Regulatory Filing Review  
Questions for 505(b)(2) Applications**

\*\*\* Note: This Appendix B not completed because we are refusing to file this application. \*\*\*

1. Does the application reference a listed drug (approved drug)? YES  NO

*If "No," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.) YES  NO

*If "Yes," skip to question 7.*

4. Is this application for a recombinant or biologically-derived product? YES  NO

*If "Yes "contact your ODE's Office of Regulatory Policy representative.*

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES  NO

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))*

*If "No," to (a) skip to question 6. Otherwise, answer part (b and (c)).*

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES  NO

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES  NO

*If "Yes," (c), list the pharmaceutical equivalent(s) and proceed to question 6.*

*If "No," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.*

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES  NO

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*If “No,” to (a) skip to question 7. Otherwise, answer part (b and (c)).*

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES  NO

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES  NO

*If “Yes,” to (c), proceed to question 7.*

**NOTE:** *If there is more than one pharmaceutical alternative approved, consult your ODE’s Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

*If “No,” to (c), list the pharmaceutical alternative(s) and contact your ODE’s Office of Regulatory Policy representative. Proceed to question 7.*

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES  NO

*If “No,” skip to question 8. Otherwise, answer part (b).*

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsules to solution”).

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES  NO

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES  NO

11. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9). YES  NO
12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) n/a YES  NO
13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

n/a – applicant is referencing the monograph

- Not applicable (e.g., solely based on published literature. See question # 7)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)  
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)  
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)  
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)  
Patent number(s):

**NOTE:** IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).  
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.  
Patent number(s):
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the

Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)  
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES  NO

*If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug*

*Was this listed drug product(s) referenced by the applicant? (see question # 2)*

YES  NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A  YES  NO

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES  NO

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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/s/

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Geraldine Smith  
4/22/2008 11:36:42 AM  
CSO



# OTC Drug Labeling Review

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**Office of Nonprescription Products**  
**Division of Nonprescription Clinical Evaluation**  
Center for Drug Evaluation and Research • Food and Drug Administration

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**NDA#:** 22-305

**Submission Date:** February 26, 2008

**Type of Submission:** New Drug Application

**Sponsor:** Niagra Pharmaceuticals, Inc. (manufacturer) through Schiff & Company (NDA holder)

**Drug Product:** Eyewash

**Active Ingredient:** •Purified water (b) (4)

**Indication:** •For cleansing the eye to help relieve irritation, (b) (4) burning, (b) (4) by removing loose foreign material. (b) (4)

**Stock Keeping Units:** (b) (4) 1 Fl. Oz. (30 ml), 4 Fl. Oz. (118 ml), 8 Fl. Oz (236 ml), 16 Fl Oz (473 ml), 16 Fl. Oz. (473 ml), 32 Fl. Oz. (946 ml))

**Review Date:** April 15, 2008

**Reviewer:** Arlene Solbeck  
Division of Nonprescription Regulation Development

**Project Manager:** Geri Smith  
Division of Nonprescription Clinical Evaluation

**Background:**

This is a new NDA for an eyewash solution that is sterilized using (b) (4).

This review addresses whether the labeling included in the sponsor's submission meets the requirements for file ability.

**Reviewer's Comments:**

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comments</b>
1	Is Index sufficient to locate necessary labeling?	Yes		
2	Has labeling for all SKUs been submitted (e.g., blister card, pouch, immediate container, carton label and package insert labeling, etc)?	Yes		
3	Does the submission contain the annotated specifications for the "Drug Facts" label?		No	
4	Is a new trade name being proposed? If multiple trade names, is the RLD trade name identified?			We don't know but the product cannot be called ' (b) (4) Eyewash", just "Eyewash"

## Any Additional Comments:

Since the sponsor is following 21 CFR 349.78(d) which specifies use of a nozzle applicator, all products must contain a nozzle applicator.

Arlene Solbeck

4/15/08

Reviewing Interdisciplinary Scientist

Date

Marina Chang

4/15/08

Supervisor/Team Leader

Date

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

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Arlene Solbeck  
4/16/2008 09:19:13 AM  
INTERDISCIPLINARY

Marina Chang  
4/16/2008 10:10:40 AM  
INTERDISCIPLINARY

# Labeling Review for Eye Wash Ophthalmic Solution

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**SUBMISSION DATES:** October 29, 2010  
March 4, 2011

**NDA/SUBMISSION TYPE:** N22-305

**ACTIVE INGREDIENTS:** Purified water USP 98.3%

**DOSAGE FORM:** Ophthalmic solution

**SPONSOR:** Niagara Pharmaceuticals, Inc. (NPI)  
60 Innovation Dr.  
Flamborough, Ontario 79H 7P3  
Canada

Robert Schiff (agent)  
Schiff & Company  
(973) 227-1830

**REVIEWER:** Elaine Abraham

**TEAM LEADER:** Marina Chang

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## I. BACKGROUND

This Eye Wash (98.3% purified water) ophthalmic solution, a sterile isotonic buffered saline solution, is submitted as an NDA because it uses (b) (4) for sterilization and is considered a new drug according to 21 CFR 310.502. This NDA was initially submitted on February 14, 2008, but because of administrative, pharmacology-toxicology, clinical, labeling, chemistry and microbiology issues, a “refuse to file” letter was issued to the sponsor.

Two issues related to labeling were included in the refuse to file letter:

- 1) If the eyewash monograph at 21 CFR § 349.78 is referenced for part of the application, the proposed product must be packaged with an eyecup or a nozzle applicator to correspond with the directions prescribed in 21 CFR § 349.78(d).

Sponsor's response in the October 29, 2010 resubmission: "The 1 ounce, 4 ounce and 8 ounce containers contain a nozzle applicator, corresponding to 21 CFR § 349.78(d). The remaining sizes, 16 and 32 ounce container closure systems are requesting approval based on 21 CFR § 330.11 NDA deviations from applicable monograph. This NDA meets all conditions of the applicable monograph except for the deviation stated above for which approval is requested. NPI Eyewash is sold by Distributors who package them with Eyecups where required. When NPI retailed these sizes we packaged them with Eyecups. NPI no longer markets Eyewash in this manner. NPI manufactures these products under private labels only."

- 2) If the Ophthalmic Drug Products for Over-the-Counter Human Use monograph (21 CFR § 349) for eyewash products is referenced to support the application, the drug product cannot be called <sup>(b) (4)</sup> [REDACTED] <sup>(b) (4)</sup> Eyewash." <sup>(b) (4)</sup> [REDACTED]

Sponsor's response in the October 29, 2010 resubmission: "The word <sup>(b) (4)</sup> [REDACTED] has been removed from all labeling."

The labels reviewed in this document are listed below. Revised labeling for all sizes was submitted on March 4, 2011 as part of the request for proprietary name review.

Submitted Labeling	Representative of Following SKUs
1 fl. oz. (30 mL) bottle	N/A
4 fl. oz. (118 mL) bottle	N/A
8 fl. oz. (236 mL) bottle	N/A
16 fl. oz. (473 mL) bottle ( horizontal layout)	N/A
16 fl. oz. (473 mL) bottle ( vertical layout)	N/A
32 fl. oz. (946 mL) bottle	N/A

## II. REVIEWER'S COMMENTS

### A. General Comments

The labels submitted are not in conformance with "Drug Facts" and the monograph for "Eye Wash" labeling requirements. The sponsor should be advised to refer to 21 CFR 201.66, 21 CFR 349.78 and applicable guidelines (*Guidance for Industry - Labeling of OTC Human Drug Products, Frequently Asked Questions, October 2001, Guidance for Industry - Labeling of OTC Human Drug Products, Small Entity Compliance Guide, May*

2009, *Guidance for Industry - Labeling of OTC Human Drug Products, Using a Column format, December 2000*) to revise their labeling and resubmit the revised labeling with the approved trade name, if available, for our review and comment. Major issues or those issues that may not be readily apparent to the sponsor are noted below.

**B. All SKUs bottle labels**

**i. Bottle Label Outside Drug Facts**

**a.**



**b. Established name and Statement of identity**

The established name of the drug is not listed on the label as required by Sec. 502(e)(1)(A)(i) of the FDCA. Also, according to 21 CFR 201.61(b), the statement of identity "... shall be in terms of the established name of the drug ... followed by an accurate statement of the general pharmacological category(ies) ...". The trade name and statement of identity should be in the following format:

Trade name  
Established name, dosage form, dosage strength  
Pharmacological category

Or

Trade name  
Established name, dosage strength  
Dosage form  
Pharmacological category

**c. Trade name**

The trade names submitted for review on March 4, 2011 are pending DMEPA review.

**d. Lot number and expiration date**

Provisions should be made for the lot or control number (21 CFR 201.18) and the expiration date (21 CFR 201.17 and 211.137(d))

**ii. Drug Facts Label**

**a. Drug Facts format**

The Drug Facts label should be revised to place labeling statements from 21 CFR 349.78 in Drug Facts format according to 21 CFR 201.66. For example:

- the indication under “**Uses**” can be revised using sub-bullets for the symptoms for better consumer understanding
- a “**Do not use**” subsection is not included in the proposed labeling, but there are statements that would appropriately fit in this subsection. For instance, the statement “you experience any open wounds in or near the eyes” should be moved from the “**Stop use and ask a doctor if**” subsection to the “**Do not use**” subsection. The intent of the warning in 21 CFR 349.78(c)(2) is that the use of the product is contraindicated in this case rather than it is an adverse event of using the product. The additional information to seek medical help that is part of this warning should be included in the product labeling. (See 21 CFR 349.78(c)(2).)

We recommend that the sponsor review all statements under 21 CFR 349.78 and determine the best way to incorporate them into Drug Facts format using available guidances described above.

**b. Age restriction** - The statement (b) (4)

(b) (4) is listed under the “**Warnings**” heading. The sponsor should provide their reasoning for this age cutoff. In addition, this is not the appropriate place for this statement as the “**Warnings**” section is generally reserved for warnings described in 201.66(c)(5)(ii)(A) through (5)(ii)(G).

**c. Tamper-evident feature** - In the “**Other information**” section, the label contains the phrase “Do not use if seal (b) (4) is broken or missing”. The tamper-evident statement on the label must be revised to include an identifying characteristic (e.g., a pattern, name, registered trademark, logo, or picture) in accordance with 21 CFR 211.132, and the identifying characteristic should be included in the tamper-evident feature.

**d. Font Specifications**

Not all font specifications have been provided to determine if the label meets format requirements listed in 21 CFR 201.66(d). The sponsor should provide annotated specifications on subheadings, barlines, hairlines, bullets, leading and characters per inch. Also, 21 CFR 201.66(d)(4) should be closely followed regarding formatting of bulleted statements.

**C. 16- and 32-fl. oz. bottles**

**i. Eyecup** - In the refusal to file letter, the sponsor was told the following based on comments in the labeling filing review:

*“If you reference the eyewash monograph at 21 CFR § 349.78 for part of the application, your proposed product must be packaged with an eyecup or a nozzle applicator to correspond with the directions prescribed in 21 CFR § 349.78(d).”*

The sponsor responded as follows:

*“The 1 ounce, 4 ounce and 8 ounce containers contain a nozzle applicator, corresponding to 21 CFR § 349.78(d). The remaining sizes, 16 and 32 ounce container closure systems are requesting approval based on 21 CFR § 330.11 NDA deviations from applicable monograph.”*

The sponsor further noted that *“NPI Eyewash is sold by Distributors who package them with Eyecups where required. When NPI retailed these sizes we packaged them with Eyecups. NPI no longer markets Eyewash in this manner. NPI manufactures these products under private labels only.”*

This is not acceptable. The distributor labeling and final product should be identical to the approved product in the NDA with the exception of any trade dress or distributor identification information on the label. It is the responsibility of the application holder to assure that any distributor labels are identical to the approved labeling. To be in conformance with 21 CFR 349.78, the eyecup for the 16- and 32-fl. oz. bottles should be submitted to the NDA for our review. The NDA deviation from applicable monograph for this NDA is the method of sterilization of the product not the omission of the eyecup/nozzle, which is required by the monograph.

- ii. Directions** - The directions for all SKUs are written as if the product will be used with a nozzle applicator. It is unclear to this reviewer whether the 16-fl. oz. and the 32-fl. oz. SKUs will be used with an eyecup or nozzle. The sponsor needs to identify the appropriate apparatus that will accompany each SKU when resubmitting labeling and revise the directions of use in Drug Facts format.

### III. RECOMMENDATIONS

We currently recommend a Complete Response action pending the resolution of the labeling deficiencies listed below. These deficiencies are based on our preliminary labeling review. Labeling should be revised and resubmitted for our review and comment.

#### A. 1-, 4-, 8-, 16- and 32-fl. oz. bottles

- The label is not in conformance with Drug Facts and monograph labeling requirements and other FDA regulations. The labeling must be revised and resubmitted for our review and comment. Refer to 21 CFR 349.78 for labeling content requirement, 21 CFR 201.66 and applicable guidelines (*Guidance for Industry - Labeling of OTC Human Drug Products, Frequently Asked Questions, October 2001, Guidance for Industry - Labeling of OTC Human Drug Products, Small Entity Compliance Guide, May 2009, Guidance for Industry - Labeling of OTC*

*Human Drug Products, Using a Column format, December 2000*) for “Drug Facts” format and layout requirements.

- The established name of the drug is not listed on the label as required by Sec. 502(e)(1)(A)(i) of the FDCA. The statement of identity should be revised in accordance with 21 CFR 201.61(b), which states that the statement of identity “shall be in terms of the established name of the drug...followed by an accurate statement of the general pharmacological category(ies)”, as follows:

Trade name  
Established name, dosage form, dosage strength  
Pharmacological category

Or

Trade name  
Established name, dosage strength  
Dosage form  
Pharmacological category

- Provisions should be made for the lot or control number (21 CFR 201.18) and the expiration date (21 CFR 201.17 and 211.137(d)).
- The Drug Facts label should be revised to place labeling statements from 21 CFR 349.78 in Drug Facts format according to 21 CFR 201.66. For example:
  - the indication under “**Uses**” can be revised using sub-bullets for the symptoms for better consumer understanding.
  - a “**Do not use**” subsection is not included in the proposed labeling, but there are statements that would appropriately fit in this subsection. For instance, the statement “you experience any open wounds in or near the eyes” should be moved from the “**Stop use and ask a doctor if**” subsection to the “**Do not use**” subsection. The intent of the warning in 21 CFR 349.78(c)(2) is that the use of the product is contraindicated in this case rather than it is an adverse event of using the product. The additional information to seek medical help that is part of this warning should be included in the product labeling. (See 21 CFR 349.78(c)(2).)

We recommend that you review all labeling statements under 21 CFR 349.78 and determine the best way to incorporate them into Drug Facts format using the available guidances described above.

- The statement “ (b) (4)  
 is listed under the “**Warnings**” heading. Provide your rationale for this age cutoff. In addition, this is not the appropriate place for this statement as the

“**Warnings**” section is generally reserved for warnings described in 201.66(c)(5)(ii)(A) through (5)(ii)(G).

- In the “**Other information**” section, the label contains the phrase “Do not use if seal (b) (4) is broken or missing”. The tamper-evident statement on the label must be revised to include an identifying characteristic (e.g., a pattern, name, registered trademark, logo, or picture) in accordance with 21 CFR 211.132, and the identifying characteristic should be included in the tamper-evident feature.
- Not all font specifications have been provided to determine if the label meets format requirements listed in 21 CFR 201.66(d). Provide annotated specifications on subheadings, barlines, hairlines, bullets, leading and characters per inch. Also, 21 CFR 201.66(d)(4) should be closely followed regarding formatting of bulleted statements.

#### **B. 16- and 32-fl. oz. bottles**

- Any distributor labeling and final product should be identical to the approved labeling and product in the NDA with the exception of trade dress or distributor identification information on the label. It is the responsibility of the application holder to assure that any distributor labels are identical to the approved labeling. To be in conformance with 21 CFR 349.78, either an eyecup or nozzle with appropriate directions for use for the 16- and 32-fl. oz. bottles must be submitted to the NDA for our review and comment.
- It is unclear which apparatus (eyecup or nozzle) will be attached to these SKUs. The directions in the currently submitted draft labels are written as if these products will be used with a nozzle applicator. Yet, under the chemistry section of the NDA, it is purported that an eyecup will be used for one of these SKUs. Identify the appropriate apparatus for each SKU, and revise the directions for use, in Drug Facts format, according to the attached apparatus. Resubmit the labeling for our review and comment.

Issue a communication to the sponsor that includes these deficiencies in order to initiate labeling negotiations.

#### **IV. SUBMITTED LABELING**

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

6 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/  
-----

ELAINE E ABRAHAM  
04/07/2011

MARINA Y CHANG  
04/07/2011

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # 022305 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Eye Wash Established/Proper Name: Purified Water Dosage Form: Solution Strengths: 98.3%		
Applicant: Niagara Pharmaceuticals Inc. Agent for Applicant (if applicable): Dr. Robert Schiff, Schiff & Company		
Date of Application: October 29, 2010 Date of Receipt: November 1, 2010 Date clock started after UN:		
PDUFA Goal Date: September 1, 2011	Action Goal Date (if different): n/a	
Filing Date: December 30, 2010	Date of Filing Meeting: December 6, 2010	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 5		
Proposed indication(s)/Proposed change(s): For flushing the eye to remove loose foreign material		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i><b>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:</b></i> <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html</a> <i><b>and refer to Appendix A for further information.</b></i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i><b>If the application includes a complete response to pediatric WR, review classification is Priority.</b></i>		
<i><b>If a tropical disease priority review voucher was submitted, review classification is Priority.</b></i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input checked="" type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>  N/A Not a Part 3 combination product  <i><b>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</b></i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input checked="" type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division ( <i>if OTC product</i> ): Division of Anti-infective and Ophthalmology Products				
List referenced IND Number(s): None				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov/CDER/OfficeofBusinessProcessSupport/ucm163970.htm">http://inside.fda.gov/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid  <input type="checkbox"/> Exempt (orphan, government)  <input checked="" type="checkbox"/> Waived (e.g., small business, public health)  <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears  <input type="checkbox"/> In arrears</p>																			
<p><b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p>		<p>X</p>																		
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <b>Check the Electronic Orange Book at:</b>  <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="201 1430 1349 1566"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration														<p>X</p>		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p><b>Exclusivity</b></p> <p>Does another product have orphan exclusivity for the same indication? <b>Check the Electronic Orange Book at:</b>  <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a></p>	<p><b>YES</b></p>	<p><b>NO</b></p> <p>X</p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																

<p><b>If another product has orphan exclusivity</b>, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p>				
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><b>If yes, # years requested:</b></p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>		X		
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p><b>If yes</b>, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input type="checkbox"/> All electronic <input checked="" type="checkbox"/> Mixed (paper/electronic)  <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p><b>If mixed (paper/electronic) submission</b>, which parts of the application are submitted in electronic format?</p>	Cover Letter Form 356h Content of labeling 32 oz. container label with Drug Facts.			
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>If electronic submission</b>, does it follow the eCTD guidance?<sup>1</sup>  <b>If not</b>, explain (e.g., waiver granted).</p>			X	
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2</p>	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

(BLAs/BLA efficacy supplements) including:  <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)  <b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?  <b>If yes, BLA #</b>				
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?  <i>If foreign applicant, both the applicant and the U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?  <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>  <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>			X	No clinical or bioequivalence studies submitted
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?  <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>  <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>			X	No clinical or bioequivalence studies submitted
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with	X			

authorized signature?  <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i>  <i>Note: Debarment Certification should use wording in FD&amp;C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>				
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?  <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i>  <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	X			

<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?  <i>If yes, date consult sent to the Controlled Substance Staff:</i>  <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>			X	

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>PREA</b>  Does the application trigger PREA?  <i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i>  <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				Pending PHMS determination if PREA is triggered

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<b>If the application triggers PREA</b> , are the required pediatric assessment studies or a full waiver of pediatric studies included?				
<b>If studies or full waiver not included</b> , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?  <i>If no, request in 74-day letter</i>				
<b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)  <i>If no, request in 74-day letter</i>				
<b>BPCA (NDAs/NDA efficacy supplements only):</b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>		X		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>		X		Sponsor was notified to submit proprietary name.
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox</i>		X		
<b>Prescription Labeling</b>	<input checked="" type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request in 74-day letter.</i>				
Is the PI submitted in PLR format? <sup>4</sup>				

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?				
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send <i>WORD</i> version if available)				
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?				
<b>OTC Labeling</b>	<input type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input checked="" type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	X			
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	X			
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	X			
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			X	
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)  <i>If yes, specify consult(s) and date(s) sent:</i>		X		
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b> <i>If yes, distribute minutes before filing meeting</i>		X		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> <i>If yes, distribute minutes before filing meeting</i>		X		
Any Special Protocol Assessments (SPAs)?		X		

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<b>Date(s):</b> <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				
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ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** Dec 6, 2010

**BLA/NDA/Supp #:** 022305

**PROPRIETARY NAME:** Eye Wash

**ESTABLISHED/PROPER NAME:** Purified water

**DOSAGE FORM/STRENGTH:** Solution/98.3%

**APPLICANT:** Niagara Pharmaceuticals Inc.

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):**

**BACKGROUND:** This product was marketed for several years without an NDA. The sponsor claimed the product met the monograph for eyewashes. However, this NDA is for an eyewash that is sterilized by (b)(4). Under 21 CFR 310. (b)(4), all drugs that are (b)(4), which would include this over-the-counter eyewash, require a New Drug Application. The collaborative review division for this application is the Division of Anti-Infective and Ophthalmology Products. This is a resubmission after refusal to file in 2008.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Phong Do	Y
	CPMS/TL:	Melissa Furness	Y
Cross-Discipline Team Leader (CDTL)	Lesley Furlong		Y
Clinical	Reviewer:	Victor Alexander -DNCE	Y
		Jennifer Harris -DAIOP	Y
	TL:	Lesley Furlong -DNCE William Boyd -DAIOP	Y Y
Social Scientist Review (for OTC products)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (for OTC products)	Reviewer:	Elaine Abraham	N
	TL:	Marina Chang	Y
Clinical Microbiology (for antimicrobial products)	Reviewer:	N/A	
	TL:	N/A	

Clinical Pharmacology	Reviewer:	N/A	
	TL:	N/A	
Biostatistics	Reviewer:	N/A	
	TL:	N/A	
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Wafa Harrouk	Y
	TL:		
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Muthu Ramaswamy	Y
	TL:	Swapan De	Y
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:	Pending	N
	TL:		
CMC Labeling Review	Reviewer:	Per CMC	
	TL:		
Facility Review/Inspection	Reviewer:	Per CMC	
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Yelena Maslov	N
	TL:	Zach Oleszczuk	N
OSE/DRISK (REMS)	Reviewer:	N/A	
	TL:	N/A	
OC/DCRMS (REMS)	Reviewer:	N/A	
	TL:	N/A	

Bioresearch Monitoring (DSI)	Reviewer:	N/A	
	TL:	N/A	
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
Other reviewers			
Other attendees	Andrea Leonard-Segal, Director, DNCE Joel Schiffenbauer, Dep. Director, DNCE Mary Vienna, Reg. Proj. Manager, DNCE Wiley Chambers, Director, DAIOP		Y Y Y Y

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b> No Clinical studies Submitted</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> <li>○ <i>this drug/biologic is not the first in its class</i></li> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	
<ul style="list-style-type: none"> <li>• Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter

<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p style="padding-left: 40px;">If no, was a complete EA submitted?</p> <p style="padding-left: 40px;">If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</li> </ul> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<b><u>CMC Labeling Review</u></b>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
<b>REGULATORY PROJECT MANAGEMENT</b>	
<b>Signatory Authority:</b> Andrea Leonard-Segal, M.D.	
<b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):	
Comments:	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  <input type="checkbox"/> No review issues have been identified for the 74-day letter.  <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):  <u>Review Classification:</u>  <input checked="" type="checkbox"/> Standard Review  <input type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> <li>notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> </ul>

<input type="checkbox"/>	<ul style="list-style-type: none"> <li>• notify DMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action (BLAs/BLA supplements only) [These sheets may be found at:  <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822</a>]</p>
<input type="checkbox"/>	Other

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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PHONG D DO  
12/17/2010

# Filing Checklist for Eye Wash Ophthalmic Solution

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**SUBMISSION DATES:** October 29, 2010

**NDA/SUBMISSION TYPE:** N22-305

**ACTIVE INGREDIENTS:** Purified water USP 98.3%

**DOSAGE FORM:** Ophthalmic solution

**SPONSOR:** Niagara Pharmaceuticals, Inc. (NPI)  
60 Innovation Dr.  
Flamborough, Ontario 79H 7P3  
Canada

Robert Schiff (agent)  
Schiff & Company  
(973) 227-1830

**REVIEWER:** Elaine Abraham

**TEAM LEADER:** Marina Chang

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<b>Submitted Labeling</b>	<b>Representative of Following SKUs</b>
1 fl. oz. (30 mL) bottle	N/A
4 fl. oz. (118 mL) bottle	N/A
8 fl. oz. (236 mL) bottle	N/A
16 fl. oz. (473 mL) bottle ( horizontal layout)	N/A
16 fl. oz. (473 mL) bottle ( vertical layout)	N/A
32 fl. oz. (946 mL) bottle	N/A

Issues	Yes/No	Comments
Is the supplement correctly assigned as a PA, CBE0, CBE30?	N/A	NDA resubmission following refusal to file
Are the outer container and immediate container labels, and consumer information leaflet and other labeling included for all submitted SKUs?	Yes	Immediate container labels for bottles submitted.
If representative labeling is submitted, does the submitted labeling represent only SKUs of different count sizes (same flavor and dosage form)?	N/A	
Is distributor labeling included?	No	
Does the submission include the annotated specifications for the Drug Facts label?	Yes	
Is Drug Facts title and Active ingredient/Purpose section of Drug Facts label visible at time of purchase?	Yes	
Do any of the labels include “prescription strength” or similar statements?	No	
Do any of the labels include “#1 doctor recommended” or similar endorsement statements?	No	
Do any labels include text in a language other than English?	No	
Is a new trade name being proposed? If multiple trade names, is the primary or preferred trade name identified?	No	There is no trade name - just “Eye Wash” on PDP.
Does a medical officer need to review any clinical issues?	Yes	
If SLR, should ONDQA also review?	N/A	

### Reviewer’s comments:

In the refusal to file letter, the sponsor was told the following based on comments in the labeling filing review:

*“If you reference the eyewash monograph at 21 CFR § 349.78 for part of the application, your proposed product must be packaged with an eyecup or a nozzle applicator to correspond with the directions prescribed in 21 CFR § 349.78(d).”*

The sponsor responded as follows:

*“The 1 ounce, 4 ounce and 8 ounce containers contain a nozzle applicator, corresponding to 21 CFR § 349.78(d).”*

*The remaining sizes, 16 and 32 ounce container closure systems are requesting approval based on 21 CFR § 330.11 NDA deviations from applicable monograph.”*

The acceptability of the 16- and 32- fl. oz. packaging sizes will be a review issue.

The sponsor further noted that *“NPI Eyewash is sold by Distributors who package them with Eyecups where required. When NPI retailed these sizes we packaged them with Eyecups. NPI no longer markets Eyewash in this manner. NPI manufactures these products under private labels only.”*

**Information Request:** No information related to labeling is needed at this time.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ELAINE E ABRAHAM  
11/23/2010

MARINA Y CHANG  
11/23/2010