

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022305Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/10 See OMB Statement on Page 3.	
PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		NDA NUMBER 22-305	
		NAME OF APPLICANT/NDA HOLDER Niagara Pharmaceuticals Inc.	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) Eye Wash			
ACTIVE INGREDIENT(S) Purified Water, USP		STRENGTH(S) 98.3%	
DOSAGE FORM Topical Ophthalmic Solution			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by FDA for listing a patent in the Orange Book.			
For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
1. GENERAL			
a. United States Patent Number		b. Issue Date of Patent	c. Expiration Date of Patent
d. Name of Patent Owner		Address (of Patent Owner)	
		City/State	
		ZIP Code	FAX Number (if available)
		Telephone Number	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)		Address (of agent or representative named in 1.e.)	
		City/State	
		ZIP Code	FAX Number (if available)
		Telephone Number	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes	<input type="checkbox"/> No
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes	<input type="checkbox"/> No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Patent Claim Number(s) (as listed in the patent) Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

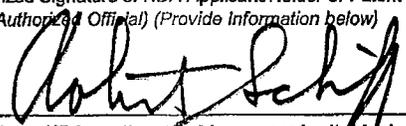
5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6 Declaration/Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below) 	Date Signed <p style="font-size: 1.2em; margin: 0;">Oct. 20, 2010</p>
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NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Robert Schiff	
Address 1129 Bloomfield Avenue	City/State West Caldwell, NJ
ZIP Code 07006	Telephone Number 973-227-1830
FAX Number (if available) 973-227-5330	E-Mail Address (if available) schiffandcompany@aol.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
 Food and Drug Administration
 Office of Chief Information Officer (HFA-710)
 5600 Fishers Lane
 Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

EXCLUSIVITY SUMMARY

NDA # 22305

SUPPL #

HFD #

Trade Name Pur-Wash

Generic Name purified water 98.3%

Applicant Name Niagara Pharmaceuticals, Inc.

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 016734

Sterile water for irrigation

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

Investigation #2

!

YES

! NO

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

=====

Name of person completing form: Phong Do, PharmD
Title: Regulatory Project Manager
Date: 9/1/11

Name of Office/Division Director signing form: Joel Schiffenbauer, M.D.
Title: Deputy Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

PHONG D DO
09/09/2011

JOEL SCHIFFENBAUER
09/12/2011



NDA 022305

INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Niagara Pharmaceuticals, Inc.
Attention: Robert Schiff
Authorized U.S. Agent
1129 Bloomfield Avenue
West Caldwell, NJ 07006

Dear Dr. Schiff:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Pur-Wash (purified water) ophthalmic solution, 98.3 %.

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by Cetero Research in Houston, Texas (Cetero).¹ The pervasiveness and egregious nature of the violative practices by Cetero has led FDA to have significant concerns that the bioanalytical data generated at Cetero from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or “prep” run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or “prep” runs that prevented Cetero and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by Cetero Research in Houston, Texas during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is searching available documentation to determine which NDAs are impacted by the above findings.

¹ These violations include studies conducted by Bioassay Laboratories and BA Research International specific to the Houston, Texas facility.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by Cetero Research in Houston, Texas during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have any questions, call Phong Do, Regulatory Project Manager, at (301) 796-4795.

Sincerely,

{See appended electronic signature page}

Andrea Leonard-Segal, M.D., M.S.
Director
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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

/s/

MELISSA H FURNESS

09/15/2011

Signing for Dr. Andrea Leonard-Segal

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 022305 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Eye Wash Established/Proper Name: Purified Water Dosage Form: Solution		Applicant: Niagara Pharmaceuticals Inc. Agent for Applicant (if applicable): Dr. Robert Schiff, Schiff & Company
RPM: Phong Do		Division: Division of Nonprescription Clinical Evaluation
<p>NDA: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(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). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s): None</p> <p>Provide a brief explanation of how this product is different from the listed drug. 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</p> <p>If no listed drug, explain. <input type="checkbox"/> This application relies on literature. <input checked="" type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> Other (explain)</p> <p><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check: 9/1/11</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>September 1, 2011</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input type="checkbox"/> None Refuse to File 4/25/2008

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<p><input type="checkbox"/> Received</p>
<p>❖ Application Characteristics²</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 5</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input checked="" type="checkbox"/> Direct-to-OTC </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </p> <p> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p> BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies </p> <p> REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> REMS not required </p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<p><input type="checkbox"/> Yes, dates</p>
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>❖ Public communications (<i>approvals only</i>)</p>	
<p>• Office of Executive Programs (OEP) liaison has been notified of action</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>• Press Office notified of action (by OEP)</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>• Indicate what types (if any) of information dissemination are anticipated</p>	<p> <input type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other </p>

² Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input checked="" type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	9/12/11
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) Approval 9/1/11
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	Over-the-Counter Medication
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

³ Fill in blanks with dates of reviews, letters, etc.
Version: 8/25/10

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. • Original applicant-proposed labeling • Example of class labeling, if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) • Most-recent draft labeling 	
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	Acceptability 6/21/11 6/21/11
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA 6/21/11 <input type="checkbox"/> DRISK <input type="checkbox"/> DDMAC <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews DNRD 4/7/11 Labeling Meeting 7/18/11
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	4/22/10; 12/17/10 <input type="checkbox"/> Not a (b)(2) 8/11/11 <input type="checkbox"/> Not a (b)(2) 8/23/11
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>PREA not triggered</u> • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>) 	<input checked="" type="checkbox"/> Verified, statement is acceptable
<ul style="list-style-type: none"> ❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>) 	4/25/08; 11/17, 11/23/10; 1/7/, 3/2, 4/13, 4/22, 5/12, 5/13, 6/24/11

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.
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❖ Internal memoranda, telecons, etc.	4/12/11 - CMC memo re: DR letter
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• EOP2 meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 9/1/11
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7/20/11
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	7/20/11
• Clinical review(s) (<i>indicate date for each review</i>)	6/23/11 DNCE; 5/10/11 DAIOP
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input checked="" type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	No clinical investigations - Filing review 12/17/10
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management	
• REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)	
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	
• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested

⁵ Filing reviews should be filed with the discipline reviews.
Version: 8/25/10

Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Biostatistics <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Statistical Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Clinical Pharmacology <input checked="" type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
❖ DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of DSI letters)</i>	<input type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 6/7/11
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary <i>(include copies of DSI letters)</i>	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 2/23/11, 7/1/11
❖ Microbiology Reviews	<input type="checkbox"/> Not needed 8/26/11
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input type="checkbox"/> None

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	2/23/11; 7/1/11 CMC Review
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶</i>)	Date completed: 1/18/11 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁶ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.
Version: 8/25/10

Appendix to Action Package Checklist

An NDA or NDA supplemental 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) **Or** 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.
- (3) **Or** 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) **And** 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.
- (3) **And** 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) **Or** 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.
- (3) **Or** 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 ADRA.

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/s/

PHONG D DO
09/12/2011

Do, Phong

From: Do, Phong
Sent: Thursday, August 25, 2011 3:43 PM
To: rschiff13@aol.com; 'TomatSchiff@aol.com'
Subject: NDA 22305;Pur-Wash; Labeling Comments

Dr. Schiff,

Please refer to your New Drug Application (NDA) dated October 28, 2010, received November 1, 2010, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Pur-Wash (purified water, 98.3%) ophthalmic solution.

We also acknowledge receipt of your amendments dated August 22 and August 24, 2011.

We have reviewed any proposed labeling changes included in the submissions and have identified the following deficiencies:

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:

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.”).

Labeling should be revised and resubmitted for our review and comment. Please confirm receipt of this email and provide an estimate of when we may expect to receive revised labeling.

Thank you,

Phong Do, PharmD

Lieutenant - USPHS

Regulatory Project Manager

FDA/CDER/ODEIV/DNCE

Phone 301-796-4795

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/s/

PHONG D DO
08/25/2011

Do, Phong

From: Do, Phong
Sent: Tuesday, August 23, 2011 3:52 PM
To: 'TomatSchiff@aol.com'; rschiff13@aol.com
Subject: NDA 22305; Pur-Wash; Information Request

Importance: High

Follow Up Flag: Follow up
Flag Status: Red

Dr. Schiff,

Please refer to your New Drug Application (NDA) dated October 28, 2010, received November 1, 2010, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Pur-Wash (purified water, 98.3%) ophthalmic solution.

We request the following clarification:

The lot used for the verification study that received the (b) (4) dose on 8/4/11 is the same lot that received the routine dose of NLT (b) (4) in May 2011 (11NP0012C). Were the units (b) (4) on 8/4/11 already sterilized on 21 May 2011? Please clarify.

Please confirm receipt of this email and provide a response as soon as possible.

Thank you,

Phong Do, PharmD

Lieutenant - USPHS

Regulatory Project Manager
FDA/CDER/ODEIV/DNCE
Phone 301-796-4795

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/s/

PHONG D DO
08/26/2011

Do, Phong

From: TomatSchiff@aol.com
Sent: Thursday, August 18, 2011 8:12 AM
To: Do, Phong; rschiff13@aol.com
Cc: rjames@niagarapharmaceuticals.com; steve@niagarapharmaceuticals.com;
r.ripenburg@niagarapharmaceuticals.com
Subject: Re: NDA 22305; Pur-Wash; Labeling comments

Dear Phong,

We confirm receipt of the labeling revisions. I have forwarded them to Niagara and will get back to you with a date as to when we will submit to revised labeling. I anticipate it should not take longer than a day or two.

Tom

Thomas Padula
Vice President of Regulatory Compliance
Schiff & Company, Inc.
1129 Bloomfield Avenue
West Caldwell, NJ 07006

Tel 973-227-1830
Fax 973-227-5330
Cell (b) (6)

www.SchiffandCompany.com

Celebrating 29 years (1982-2011) of service in Compliance, Regulatory Affairs and Clinical Research

**In a message dated 8/18/2011 7:33:10 A.M. Eastern Daylight Time,
Phong.Do@fda.hhs.gov writes:**

Dr. Schiff,

Please refer to your New Drug Application (NDA) dated October 28, 2010, received November 1, 2010, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Pur-Wash (purified water, 98.3%) ophthalmic solution.

We also acknowledge receipt of your amendment dated August 17, 2011.

We have reviewed any proposed labeling changes included in the submissions and have identified the following deficiencies:

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.

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.

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.

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.

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”.

Labeling should be revised and resubmitted for our review and comment. Please confirm receipt of this email and provide an estimate of when we may expect to receive revised labeling.

Thank you,

Phong Do, PharmD

Lieutenant - USPHS

Regulatory Project Manager

FDA/CDER/ODEIV/DNCE

Phone 301-796-4795

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

/s/

PHONG D DO
08/18/2011

Do, Phong

From: Rschiff13@aol.com
Sent: Friday, August 05, 2011 9:31 AM
To: Do, Phong
Cc: steve@niagarapharmaceuticals.com; TomatSchiff@aol.com; rjames@niagarapharmaceuticals.com
Subject: Re: NDA 22305; Pur-Wash; Follow up re: August 3, 2011 Tcon

Hi Phong,

Thanks for the information.

All the best and have a good weekend,

Bob

**Robert Schiff, PhD, RAC, CQA, FRAPS
President and CEO
Schiff & Company, Inc.
1129 Bloomfield Avenue
West Caldwell, NJ 07006**

**Tel 973-227-1830
Fax 973-227-5330
Cell [REDACTED] (b) (6)**

www.SchiffandCompany.com

Celebrating 29 years (1982-2011) of service in Compliance, Regulatory Affairs and Clinical Research

**In a message dated 8/5/2011 9:24:17 A.M. Eastern Daylight Time,
Phong.Do@fda.hhs.gov writes:**

Dr. Schiff,

As promised, I am sending you an electronic record of the advice/information requests that the Agency communicated to you verbally during our August 3, 2011 telephone conversation.

Attendees for this teleconference were as follows:

FDA Representatives

**Phong Do, Regulatory Project Manager
Melissa Furness, Chief, Project Management Staff
James McVey, Microbiology Team Leader
Denise Miller, Microbiology Reviewer**

Niagara Pharmaceuticals, Inc. Representatives

**Robert Schiff, President, Schiff & Company, Inc.
Thomas Padula, Vice President of Regulatory Compliance, Schiff & Company, Inc.
Steve Leistner, CEO, Niagara Pharmaceuticals, Inc.**

Reesa James, Quality Manager, Niagara Pharmaceuticals, Inc.

The following advice and information requests were discussed:

- 1) According to your report, the (b) (4) method you are using is (b) (4) which is a bioburden based validation of the (b) (4) process. When you stated that your (b) (4) dosage for the eye cups is based on a previous (b) (4) validation study, was that study on the liquid bottle bioburden or on the eye cups bioburden? What is the bioburden level and bioburden population that you have based your (b) (4) dosage?
- 2) To satisfy the (b) (4) guidelines for (b) (4) you must perform your verification dose experiment on (b) (4) units for sterility on the highest average bioburden lot with the minimum calculated (b) (4) dose. This is to verify your minimum (b) (4) dose used for routine (b) (4) or the eyecups is correct. Increase your sample size to (b) (4) units to verify this.
- 3) In your final report, justify your (b) (4) dosage based on bioburden. Provide the bioburden data and calculations used to arrive at your (b) (4) dose.
- 4) According to USP <71> sterility test for release, you should test 10 samples per media. Since there are two media, you should test 20 eyecups.
- 5) Your protocol acceptance criteria for your (b) (4) levels should be stated as the range that was targeted for your validation levels to support your production dose of a minimum of (b) (4)

In closing, you stated that you will provide a response addressing the above advice/information requests by COB August 22, 2011.

Regards,

Phong Do, PharmD

Lieutenant - USPHS

Regulatory Project Manager

FDA/CDER/ODEIV/DNCE

Phone 301-796-4795

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/s/

PHONG D DO
08/07/2011

Do, Phong

From: Do, Phong
Sent: Friday, July 29, 2011 11:19 AM
To: rschiff13@aol.com
Cc: 'TomatSchiff@aol.com'
Subject: NDA 22305; Pur-Wash; Labeling comments

Follow Up Flag: Follow up
Flag Status: Red

Dr. Schiff,

Please refer to your New Drug Application (NDA) dated October 28, 2010, received November 1, 2010, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Pur-Wash (purified water, 98.3%) ophthalmic solution.

We also acknowledge receipt of your amendments dated April 18, April 26, May 9, May 11, May 18, May 31, and July 6, 2011.

We have reviewed any proposed labeling changes included in the submissions and have identified the following deficiencies:

- 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 should 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 (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 (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] (b)(4)” by preceding the word (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. Revise the format to include bulleted statements 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 (b)(4)). Remove (b)(4) 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 based on our review:

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).

Labeling should be revised and resubmitted for our review and comment. Please confirm receipt of this email and provide an estimate of when we may expect to receive revised labeling.

Thank you,

Phong Do, PharmD

Lieutenant - USPHS

Regulatory Project Manager

FDA/CDER/ODEIV/DNCE

Phone 301-796-4795

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/s/

PHONG D DO
08/01/2011

Do, Phong

From: Do, Phong
Sent: Friday, June 24, 2011 1:03 PM
To: 'Rschiff13@aol.com'
Cc: 'TomatSchiff@aol.com'
Subject: NDA 22305; Pur-wash; eye wash; Information Request

Follow Up Flag: Follow up
Flag Status: Red

Dr. Schiff,

We are in the process of reviewing NDA 22305 and request that you provide the following information by July 1, 2011:

Your November 29, 2010 response to FDA's Information Request for NDA 22-305 dated November 17, 2010 included the following information for the safety summary in Module 5.3.5:

“From June 3, 2003 through November 25, 2010 approximately (b)(4) units were sold in the US and Canada. As of the spring of 2007 all units sold were in Canada because an NDA was being filed in the US. However, prior to that time about (b)(4) units were sold in the US.”

Please provide a summary by individual container size (1 oz, 4 oz, 8 oz, 16 oz, and 32 oz) for the total number (and percentage) of all units ((b)(4) units) sold from June 3, 2003 through November 25, 2010. Please provide a separate summary for U.S. sales ((b)(4) units) for the period June 3, 2003 until the spring of 2007.

Please confirm receipt of this information request.

Best Regards,

Phong Do, PharmD

Lieutenant - USPHS

Regulatory Project Manager
FDA/CDER/ODEIV/DNCE
Phone 301-796-4795

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/s/

PHONG D DO
06/24/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 022305

**PROPRIETARY NAME REQUEST
ACCEPTABLE**

Niagara Pharmaceuticals, Inc.
c/o Schiff & Company
1129 Bloomfield Avenue
West Caldwell, New Jersey 07006

ATTENTION: Robert Schiff
President, Schiff & Company

Dear Mr. Schiff:

Please refer to your New Drug Application (NDA) dated October 28, 2010, received November 1, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Purified Water Ophthalmic Solution, 98.3%.

We also refer to your May 11 2011, correspondence, received May 12, 2011, requesting review of your proposed proprietary name, Pur-Wash. We have completed our review of the proposed proprietary name, Pur-Wash, and have concluded that it is acceptable.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Cheryle Milburn, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2084. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Phong Do at (301) 796-4795.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
06/21/2011



NDA 022305

**PROPRIETARY NAME REQUEST
WITHDRAWN**

Niagara Pharmaceuticals, Inc.
c/o Schiff & Company
1129 Bloomfield Avenue
West Caldwell, NJ 07006

ATTENTION: Robert Schiff
President, Schiff & Company

Dear Mr. Schiff:

Please refer to your New Drug Application (NDA) dated October 28, 2010, received November 1, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Purified Water Ophthalmic Solution, 98.3%.

We acknowledge receipt of your April 26, 2011, correspondence received on April 27, 2011, notifying us that you are withdrawing your request for review of the proposed proprietary name (b) (4). This proposed proprietary name request is considered withdrawn as of April 27, 2011.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Cheryle Milburn, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2084. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Phong Do at (301) 796-4795.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
06/21/2011

Do, Phong

From: Rschiff13@aol.com
Sent: Friday, May 13, 2011 1:42 PM
To: Do, Phong
Subject: Re: NDA 22305; Eye wash; Information request
Follow Up Flag: Follow up
Flag Status: Red

Hi,

We will respond shortly.

Bob

**Robert Schiff, PhD, RAC, CQA, FRAPS
President and CEO
Schiff & Company, Inc.
1129 Bloomfield Avenue
West Caldwell, NJ 07006**

**Tel 973-227-1830
Fax 973-227-5330
Cell (b)(6)**

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**In a message dated 5/13/2011 1:40:58 P.M. Eastern Daylight Time,
Phong.Do@fda.hhs.gov writes:**

Dr. Schiff

We are in the process of reviewing NDA 22305 and request that you provide the following information:

- 1) The (b)(4) hold time study of the formulated bulk provided in report PQ-EWB4-2006 was performed with lots 6NP0109, 7NP0002C and 7NP0005. These lots appear to be the preserved formulation and therefore the results of this study are not supportive of a (b)(4) hold time with the current formulation. Provide the hold time study using the unpreserved formulation to support a (b)(4) bulk hold time or provide clarifications.
- 2) In report PQ-TK-04/05EW8500-2010 page 21 of 31 in Table 17-1A, the microbial bioburden result for Lot 10NP0009 was recorded as (b)(4) for both the (b)(4) counts. The specification is less than or equal to (b)(4). The result as recorded does not support a passing result nor is it consistent with the results of the other two lots tested. The other lots are recorded as (b)(4). Please justify.

We also ask that you provide us with a projected submission timeline for the information requested above.

Please confirm receipt of this information request.

Best regards,

Phong Do, PharmD

Lieutenant - USPHS

Regulatory Project Manager

Division of Nonprescription Clinical Evaluation

Office of Drug Evaluation IV

CDER/FDA

10903 New Hampshire Avenue

Bldg. 22, Room 5485

Silver Spring, MD 20993

Phone 301-796-4795

Fax 301-796-9899

Email: phong.do@fda.hhs.gov

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/s/

PHONG D DO
05/13/2011



NDA 022305

LABELING COMMENTS

Niagara Pharmaceuticals, Inc.
Attention: Robert Schiff
Authorized U.S. Agent
1129 Bloomfield Avenue
West Caldwell, NJ 07006

Dear Mr. Schiff:

Please refer to your October 29, 2010 New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Eye Wash (98.3% purified water) ophthalmic solution.

We also refer to our January 7, 2011 letter in which we notified you of our target date of July 20, 2011 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012."

On November 1, 2010, we received your October 29, 2010 submission to this application that contained your proposed labeling, and have proposed revisions that are listed below.

Proposed Revisions:

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.

Deficiencies include, but may not be limited to:

- The established name of the drug is not listed on the label as required by Sec. 502(e)(1)(A)(i) of the FFDCA. 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 the following labeling statements from 21 CFR 349.78 in Drug Facts format according to 21 CFR 201.66:
 - 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 regulatory references cited above.

- The statement (b) (4) is listed under the “**Warnings**” heading. Remove the statement or 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). To verify that you have met the requirements, provide annotated specifications on subheadings, barlines, hairlines, bullets, leading (i.e., space between two lines of text), 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 SKU's container closure systems. 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 SKU's container closure systems. Identify the apparatus you intend to use for each container closure system, and revise the directions for use, in Drug Facts format, according to the apparatus. Resubmit the labeling for our review and comment.

If you have any questions, call Phong Do, Regulatory Project Manager, at (301) 796-4795.

Sincerely,

{See appended electronic signature page}

Lesley-Anne Furlong, M.D., M.S.
Cross-Discipline Team Leader
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

LESLEYANNE A FURLONG
05/12/2011

Do, Phong

From: Rschiff13@aol.com
Sent: Friday, April 22, 2011 9:59 AM
To: Liu, Youbang
Cc: Do, Phong; tomatschiff@aol.com; steve@niagarapharmaceuticals.com; rjames@niagarapharmaceuticals.com
Subject: Re: Information Request for NDA 22305

Hi Dr. Liu,

Your question is well taken. Our offices are closed today and we will respond back with either the answer or timeline next week.

All the best and a happy weekend and holiday,

Bob

**Robert Schiff, PhD, RAC, CQA, FRAPS
CEO & President
Schiff & Company, Inc.
1129 Bloomfield Avenue
West Caldwell, NJ 07006**

Tel 973-227-1830

Fax 973-227-5330

Cell [REDACTED] (b) (6)

www.SchiffandCompany.com

Celebrating 29 years (1982-2011) of service in Compliance, Regulatory Affairs and Clinical Research

In a message dated 4/22/2011 9:55:51 A.M. Eastern Daylight Time, Youbang.Liu@fda.hhs.gov writes:

Dear Dr. Schiff,

We are in the process of reviewing NDA 22305 and request that you provide the following information:

The bulk drug substance (purified water, USP) has a microbial specification of [REDACTED] (b) (4). The bulk product has an in-process specification of [REDACTED] (b) (4). The description of the manufacturing process does not include any steps designed to reduce the bioburden from [REDACTED] (b) (4)

We also ask that you provide us with a projected submission timeline for the information requested above.

Please confirm receipt of this information request.

Kind Regards,

Youbang Liu, Ph.D.
Regulatory Project Manager
ONDQA/OPS/CDER/FDA
Division III of New Drug Quality Assessment
10903 New Hampshire Avenue
Building 21, Room 2649
Silver Spring, MD 20993
Phone: (301) 796-1926
Fax: (301) 796-9748

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/s/

PHONG D DO
04/22/2011



NDA 022305

DISCIPLINE REVIEW LETTER

Niagara Pharmaceuticals, Inc.
Attention: Robert Schiff
Authorized U.S. Agent
1129 Bloomfield Avenue
West Caldwell, NJ 07006

Dear Mr. Schiff:

Please refer to your October 28, 2010 New Drug Application (NDA) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Eye Wash (98.3% purified water) ophthalmic solution.

We also refer to your submissions dated November 29, 2010, November 30, 2010, March 3, 2011, March 4, 2011, March 15, 2011, and March 25, 2011.

Our review of the Chemistry, Manufacturing, and Controls section of your submission is complete, and we have identified the following deficiencies:

1. Your proposed commercial packaging configuration for the 16 and 32 oz immediate containers (bottles) without either an eye cup or nozzle is not acceptable and does not conform to options for drug product labeling directions as outlined in 21 CFR § 349.78(d). Therefore, for these containers, either the eye cup or the nozzle should be included with appropriate sterility testing and supportive stability data.
2. Your justification that you plan to sell these 16 and 32 oz packaging configurations to distributors who may repackage them with eye cups is not acceptable. We approve labeling and packaging configurations only for final to-be-marketed drug products.
3. The copies of (b) (4) and conductivity data (for purified water) provided in your Filing Communication Response are not legible. Please submit the (b) (4) and conductivity data for purified water batches manufactured since 2007 to date in a tabular format for Agency review.
4. Provide samples of your proposed drug product representing each of the commercial packaging configurations.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If

you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Phong Do, Regulatory Project Manager, at (301) 796-4795.

Sincerely,

{See appended electronic signature page}

Andrea Leonard-Segal, M.D., M.S.
Director
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

ANDREA LEONARD SEGAL
04/13/2011

Do, Phong

From: Rschiff13@aol.com
Sent: Wednesday, March 02, 2011 4:45 PM
To: Do, Phong
Subject: Re: NDA 22305; Eye wash; Information Request
Follow Up Flag: Follow up
Flag Status: Red

Hi Phong,

We confirm receipt and will move quickly.

All the best,

Bob

**Robert Schiff, Ph.D., RAC, CQA. FRAPS
President
Schiff & Company, Inc.
1129 Bloomfield Ave.
West Caldwell, NJ 07006**

Tel 973-227-1830

Fax 973-227-5330

Cell (b) (6)

www.SchiffandCompany.com

Celebrating 29 years (1982-2011) of service in Compliance, Regulatory Affairs and Clinical Research

**In a message dated 3/2/2011 4:09:15 P.M. Eastern Standard Time,
Phong.Do@fda.hhs.gov writes:**

Dr. Schiff,

We are in the process of reviewing NDA 22305 and request that you provide the following information:

- 1. Provide test results for all batches of purified water produced from Sep 2007 to date to demonstrate that your water purification system operates in a state of control.**
- 2. Specify the (b) (4) used in the Water Purification.**
- 3. Provide information on the levels of (b) (4) levels present in the purified water.**
- 4. Explain how sodium chloride can function (b) (4) (Table 1 of Section 3.2.P.1 and Table 3 of 3.2.P.2.1.2). If it is an error, please correct the above information.**

Reference ID: 2912830

3/3/2011

5. Include pH as an in-process control for the bulk eye wash solution.
6. Update the specification for incoming raw materials with relevant reference to USP monograph method (Section number).
7. Please confirm if the USP methods for testing raw materials and finished product are qualified.
8. Your specification for the appearance of the product (“Colorless to pale yellow liquid”) is not appropriate. Revise the specification to colorless liquid or provide complete characterization information for the pale yellow eye wash liquid.
9. Include a heavy metals specification for the finished product.
10. Provide information on the ink and adhesive used for the proposed commercial label. Also, indicate if the container labels used in the extractable leachable studies are the same as the commercial packaging material.

We also ask that you provide us with a projected submission timeline for the information requested above.

Please confirm receipt of this information request.

Best regards,

Phong Do, PharmD

Lieutenant - USPHS

Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
CDER/FDA
10903 New Hampshire Avenue
Bldg. 22, Room 5485
Silver Spring, MD 20993
Phone 301-796-4795
Fax 301-796-9899
Email: phong.do@fda.hhs.gov

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/s/

PHONG D DO
03/03/2011



NDA 022305

FILING COMMUNICATION

Niagara Pharmaceuticals, Inc.
Attention: Robert Schiff
Authorized U.S. Agent
1129 Bloomfield Avenue
West Caldwell, NJ 07006

Dear Mr. Schiff:

Please refer to your New Drug Application (NDA) dated October 28, 2010, received November 1, 2010, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Eye Wash (98.3% purified water) ophthalmic solution.

We also refer to your submissions dated November 29, 2010 and November 30, 2010.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is September 1, 2011.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by July 20, 2011.

During our filing review of your application, we identified the following potential review issues and request that you submit the following information:

1. Provide process validation (bulk solution manufacturing, filling and sterilization) data for your proposed preservative free drug product.
2. Provide endotoxin limits for the finished drug product.

3. Specify the raw materials and packaging components used in the manufacturing of the finished drug product.
4. Provide 12 months of real-time and 6-months of accelerated stability data for three batches for your proposed drug product.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Phong Do, Regulatory Project Manager, at (301) 796-4795.

Sincerely,

{See appended electronic signature page}

Joel Schiffenbauer, M.D.
Deputy Director
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

JOEL SCHIFFENBAUER
01/07/2011

Do, Phong

From: Do, Phong
Sent: Tuesday, November 23, 2010 10:46 AM
To: 'rschiff13@aol.com'
Subject: NDA 22305; Eye Wash; Information Request

Dr. Schiff,

Additional information is required for the filing review of NDA 22305. We request you provide the following information by COB November 30, 2010.

- For each establishment named in your application include the full corporate name of the facility, FEI number, specific address, contact person (name, title, phone number and email address), and specific information on the type of manufacturing operation at the facility, include the type of testing (if applicable). Each facility must be ready for inspection so that the inspection may be planned as soon as possible.

Please confirm receipt of this information request.

Phong Do, PharmD

Lieutenant - USPHS

Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
CDER/FDA
10903 New Hampshire Avenue
Bldg. 22, Room 5485
Silver Spring, MD 20993
Phone 301-796-4795
Fax 301-796-9899
Email: phong.do@fda.hhs.gov

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/s/

PHONG D DO
12/17/2010

Do, Phong

From: Do, Phong
Sent: Wednesday, November 17, 2010 2:48 PM
To: 'rschiff13@aol.com'
Subject: NDA 22305; Eye Wash; Information Request

Dr. Schiff,

We understand that you intend to rely on FDA's previous conclusions of efficacy and safety under the Ophthalmic Drug Products for Over-the-Counter Human Use monograph (21 CFR § 349) to support your eyewash product. There are additional items required for an NDA submission under 21CFR314.50 to permit substantive review.

Additional information is required in the Clinical Data section of an NDA submission under 21CFR314.50(d)(5). This information is submitted in Module 5 of the CTD format.

- Provide a summary and update of safety information, from June 3, 2003 onward, including pertinent animal data, demonstrated or potential adverse effects of the drug, clinically significant drug/drug interactions, and other safety considerations, such as data from epidemiological studies of related drugs (21CFR314.50(d)(5)(vi)(a)). This safety summary should include a description of adverse event reports from your company database, FDA AERS database, and WHO Vigibase, if any.
- Provide a description and analysis of any other data or information relevant to an evaluation of the safety and effectiveness of the drug product obtained by the applicant, including information derived from clinical investigations, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers (21CFR314.50(d)(5)(iv)).

Additional information is required in the Application Summary section of an NDA submission under section 21CFR314.50(c). This information is submitted in Module 2 of the CTD format.

- Provide a brief description of the marketing history, if any, of the drug outside the United States, including a list of the countries in which the drug has been marketed, a list of any countries in which the drug has been withdrawn from marketing for any reason related to safety or effectiveness, and a list of countries in which applications for marketing are pending. The description is required to describe both marketing by the applicant and, if known, the marketing history of other persons (21CFR314.50(c)(2)(iii)).
- Provide a concluding discussion that presents the benefit and risk considerations related to the drug, including a discussion of any proposed additional studies or surveillance the applicant intends to conduct postmarketing (21CFR314.50(c)(2)(ix)).

We believe each of these required summaries may be brief in this situation, since you intend to support your application by reference to the Ophthalmic Drug Products for Over-the-Counter Human Use monograph (21 CFR § 349).

Please provide the required summaries by close of business on December 2, 2010, so that they may be included in our filing review for NDA 22-305. We also ask that you provide us with a projected submission timeline for each request.

Please confirm receipt of this information request.

Best regards,

Phong Do, PharmD

Lieutenant - USPHS

Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
CDER/FDA
10903 New Hampshire Avenue
Bldg. 22, Room 5485
Silver Spring, MD 20993
Phone 301-796-4795
Fax 301-796-9899
Email: phong.do@fda.hhs.gov

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/s/

PHONG D DO
12/17/2010



NDA 022305

**ACKNOWLEDGE RESUBMISSION
AFTER REFUSE-TO-FILE**

Niagara Pharmaceuticals, Inc.
Attention: Robert Schiff
Authorized U.S. Agent
1129 Bloomfield Avenue
West Caldwell, NJ 07006

Dear Mr. Schiff:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act in response to our April 25, 2010 refusal to file letter for the following:

Name of Drug Product: Eye Wash (98.3% purified water) ophthalmic solution

Review Priority Classification: Standard (S)

Date of Application: October 28, 2010

Date of Receipt: November 1, 2010

Our Reference Number: NDA 022305

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 31, 2010 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be September 1, 2011

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Nonprescription Clinical Evaluation
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call Phong Do, Regulatory Project Manager, at (301) 796-4795.

Sincerely,

{See appended electronic signature page}

Melissa Hancock Furness
Chief, Project Management Staff
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

MARY RUSSELL R VIENNA
11/16/2010
signed by Melissa Hancock Furness



NDA 22-305

Schiff & Company
Attention: Robert Schiff, Ph.D., RAC, CQA(ASQ)
President
U.S. Agent for Niagara Pharmaceuticals Inc.
1129 Bloomfield Avenue
West Caldwell, NJ 07006

Dear Dr. Schiff:

Please refer to your January 30, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Eye Wash ((b) (4) purified water) ophthalmic solution.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR § 314.101(d) for the following reasons:

1. The field copy required by 21 CFR § 314.50 was not submitted.
2. The application form (Form 356h) is signed only by the foreign applicant. The U.S. agent has not signed the 356h as required by 21 CFR § 314.50(a)(5).
3. The index does not include reference to Modules 4 & 5 as required by 21 CFR § 314.50(b).
4. The summary required by 21 CFR § 314.50(c) was not submitted.
5. The field copy certification required by 21 CFR § 314.50(d)(1)(v) was not submitted.
6. The non-clinical pharmacology and toxicology section required by 21 CFR § 314.50(d)(2) contains no information except a statement that the proposed product is a monographed drug and that the monograph requirements have been met. The eyewash monograph active ingredients at 21 CFR § 349.20 referenced in your cover letter cannot be referenced to support this NDA for non-clinical pharmacology and toxicology purposes because the preliminary chemistry review for this NDA indicates that there are a number of differences between your proposed (b) (4) eyewash and the (b) (4) product listed in the Ophthalmic Drug Products for Over-the-Counter Human Use monograph (21 CFR § 349) addressing eyewash products. It appears that impurities and/or degradants may be present in your product that must be characterized.

7. The clinical section required by 21 CFR § 314.50(d)(5) contains no information except a statement that the proposed product is a monographed drug and that the monograph requirements have been met. As discussed previously during our September 6, 2007 teleconference, if the chemistry and microbiology sections of the NDA had demonstrated sterility of the product and there were no meaningful changes to the components after [REDACTED] (b) (4), then reference to the eyewash monograph could be used to support the NDA. However, multiple deficiencies in the chemistry and microbiology sections of the NDA have been found during our preliminary review, and the attributes of your proposed product appear to deviate from the Ophthalmic Drug Products for Over-the-Counter Human Use monograph (21 CFR § 349) addressing eyewash products, necessitating the submission of clinical safety and efficacy studies to support an NDA for this product.
8. The pediatric use section required by 21 CFR § 314.50(d)(7) was not submitted.
9. The patent information (including Form 3542) required by 21 CFR § 314.50(h) was not submitted.
10. The patent certification does not include the wording required by 21 CFR § 314.50(i)(1)(ii).

We have the following additional comments for your resubmission of this NDA based on our preliminary review of the application:

11. Include a comprehensive study of impurities and degradants. This characterization work should:
 - a. employ analytical technologies such as high performance liquid chromatography (HPLC), gas chromatography (GC), and mass spectrometry;
 - b. comply with ICH guideline Q3B(R) for reporting, identification, and qualification of impurities and degradants;
 - c. include a comprehensive comparison of the impurity profile [REDACTED] (b) (4); and
 - d. include monitoring of the impurity profile throughout the registration stability studies using stability-indicating methods.
12. Include a comprehensive study of extractables. The study should:
 - a. employ HPLC/mass spectrometry in addition to GC/mass spectrometry as the analytic methods;

- b. be conducted using samples packaged in the to-be-marketed container/closure systems and (b) (4) in the same manner as that for the commercial batches;
 - c. include pertinent label components (e.g., inks, adhesives, and varnishes) and appropriate controls (e.g., glass bottle) in the study;
 - d. include a comparison of the extractables profile between the (b) (4) product;
 - e. identify all extractables present at levels above 10 ppm; and
 - f. qualify all extractables present at levels above 20 ppm.
13. Add the following tests with appropriate acceptance criteria to the drug product specification:
- a. particulate matter;
 - b. minimal fill (release only);
 - c. water loss;
 - d. packaging integrity; and
 - e. osmolality.
14. The registration stability studies should comply with ICH Q1A. In addition to those tests included in the drug product specification:
- a. monitor extractables in the stability studies throughout the study period with a glass control;
 - b. include a check in antimicrobial effectiveness test (USP<51>) in the stability protocol; and
 - c. if you do not plan to conduct stability studies for each packaging configuration, refer to ICH Guideline Q1D for the proper bracketing strategy and provide a strong scientific justification.
15. The certificates of analysis (COAs) and stability data tables must contain the numerical test results or actual readings. Simply listing “pass,” “conform,” or “fail” on the COAs and stability data tables is unacceptable. We recommend that you use color standards, such as those from European Pharmacopeia, to evaluate the color of the proposed product.

16. Provide a clear description of each to-be-marketed packaging configuration, including information for each packaging component (e.g., cap, tip, dropper, space reducer, bottle, ink, adhesive, varnish).
17. Provide chemistry, manufacturing and controls information for each packaging component, or reference a Drug Master File (DMF) for each component. Refer to CDER *Guidance for Industry Container Closure Systems for Packaging Human Drugs and Biologics* for information that should be submitted in an NDA. The proposed immediate packaging components must comply with USP<661>.
18. Provide container/closure integrity validation results for all proposed container/closure configurations.
19. Tamper-resistant packaging is required for all OTC products (see 21 CFR § 211.132).
20. 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).
21.  (b) (4)
22. Include annotated font specifications for the “Drug Facts” label in accordance with 21 CFR § 201.66(d).
23. Include a User Fee Cover Sheet (Form 3397).
24. Include a Debarment Certification using the wording in the Federal Food, Drug, and Cosmetic Act Section 306(k)(1).
25. The Pediatric Research Equity Act (PREA) of 2003 requires that all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and/or new dosing regimens contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. Since your NDA proposes a new dosage form, the application is subject to the PREA requirements, and you must address the PREA requirements in your resubmission of this NDA.

We remind you that 16 C.F.R. § 314.50(d)(3) requires that you submit information supporting your request for a waiver of bioavailability studies.

You were granted a small business waiver of the application fee for this application on February 14, 2008. A reevaluation of the waiver may be required should you resubmit the application. You should contact the Office of Regulatory Policy approximately 90 days prior to resubmitting the application to determine whether the application continues to qualify for a waiver.

Within 30 days of the date of this letter, you may request in writing a meeting about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If, after the informal conference, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the informal conference. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee.

If you have any questions, contact Geri Smith, Regulatory Project Manager, at geri.smith@fda.hhs.gov or (301) 796-2204.

Sincerely,

{See appended electronic signature page}

Joel Schiffenbauer, M.D.
Deputy Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

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/s/

Joel Schiffenbauer
4/25/2008 08:23:41 AM



NDA 22-305

NDA ACKNOWLEDGMENT

Schiff & Company
Attention: Robert Schiff, Ph.D., RAC, CQA(ASQ)
President
U.S. Agent for Niagara Pharmaceuticals Inc.
1129 Bloomfield Avenue
West Caldwell, NJ 07006

Dear Dr. Schiff:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: (b) (4) Eye Wash (b) (4) purified water) ophthalmic solution

Date of Application: January 30, 2008

Date of Receipt: February 26, 2008

Our Reference Number: NDA 22-305

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 26, 2008 in accordance with 21 CFR 314.101(a).

The NDA number provided above must be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Nonprescription Products
Division of Nonprescription Clinical Evaluation
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper form should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper

size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, contact Geri Smith, Regulatory Project Manager, at geri.smith@fda.hhs.gov or (301) 796-2204.

Sincerely,

{See appended electronic signature page}

Leah Christl, Ph.D.
Acting Chief, Project Management Staff
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

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/s/

Leah Christl
3/13/2008 05:20:52 PM