

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**202736Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 202736

SUPPL #

HFD # 540

Trade Name Sklice

Generic Name (ivermectin) Lotion, 0.5%

Applicant Name Sanofi-Topaz, 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)(1)

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?

3 years

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#

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:

TOP011  
TOP012

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	TOP011	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	TOP012	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

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	TOP011	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	TOP012	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

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

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

TOP011, TOP012

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1  
IND # 073134      YES       !  
!      ! NO   
! Explain:

Investigation #2  
IND # 073134      YES       !  
!      ! NO   
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1  
YES       !  
!      ! NO   
Explain:      ! Explain:

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: Dawn Williams, B.S.N.

Title: RPM

Date: 1/23/2012

Name of Office/Division Director signing form: Susan J. Walker, M.D., F.A.A.D.

Title: Director, DDDP

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/  
-----

DAWN WILLIAMS  
01/31/2012

SUSAN J WALKER  
02/06/2012

0.5% Ivermectin Cream  
Topaz Pharmaceuticals, Inc.  
New Drug Application

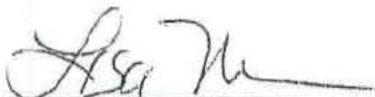
1.3.3 Debarment Certification

**1.3.3 Debarment Certification**

Topaz Pharmaceuticals Inc., hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Pursuant to Section 306(k) of the Federal Food, Drug, and Cosmetic Act, as amended by the Generic Drug Enforcement Act of 1992, Topaz Pharmaceuticals Inc., hereby certifies that we did not and will not use, in any capacity, the services of any person debarred under subsection (a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this NDA.

Topaz Pharmaceuticals Inc. certifies further that, during the previous five years, it has not sustained a conviction that is described in subsections (a) or (b) of the Generic Drug Enforcement Act of 1992. In addition, Topaz Pharmaceuticals Inc. certifies that no person affiliated with the company that was responsible for the development or submission of this application has been convicted of an offense described in subsections (a) or (b) of the Generic Drug Enforcement Act of 1992.



\_\_\_\_\_  
Lisa DeLuca, PhD

Vice President, Regulatory Affairs and  
Quality Assurance

Topaz Pharmaceuticals Inc.

1/26/2011  
\_\_\_\_\_  
Date

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 202736 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Sklice Established/Proper Name: (ivermectin) Dosage Form: Lotion		Applicant: Sanofi-Topaz, Inc. Agent for Applicant (if applicable):
RPM: Dawn Williams, B.S.N.		Division: DDDP
<p><b><u>NDA and NDA Efficacy Supplements:</u></b></p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1)    <input 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><b><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></b></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug.  <input type="checkbox"/> This application relies on literature.  <input type="checkbox"/> This application relies on a final OTC monograph.  <input type="checkbox"/> This application relies on (explain)</p> <p><b><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input type="checkbox"/> No changes    <input type="checkbox"/> Updated    Date of check:</p> <p><b>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.</b></p>
❖ Actions		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>February 7, 2012</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input type="checkbox"/> None

<sup>1</sup> 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.

<sup>2</sup> For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<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 <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a>). If not submitted, explain _____</p>	<p><input type="checkbox"/> Received</p>
<p>❖ Application Characteristics <sup>3</sup></p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority                  Chemical classification (new NDAs only):</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 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>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><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>REMS: <input type="checkbox"/> MedGuide  <input type="checkbox"/> Communication Plan  <input type="checkbox"/> ETASU  <input type="checkbox"/> MedGuide w/o REMS  <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>	
<ul style="list-style-type: none"> <li>Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>
<ul style="list-style-type: none"> <li>Press Office notified of action (by OEP)</li> </ul>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<p><input checked="" type="checkbox"/> None  <input type="checkbox"/> HHS Press Release  <input type="checkbox"/> FDA Talk Paper  <input type="checkbox"/> CDER Q&amp;As  <input type="checkbox"/> Other</p>

<sup>3</sup> 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"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>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></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA #        and date exclusivity expires:
<ul style="list-style-type: none"> <li>(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></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #        and date exclusivity expires:
<ul style="list-style-type: none"> <li>(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></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #        and date exclusivity expires:
<ul style="list-style-type: none"> <li>(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></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #        and date exclusivity expires:
<ul style="list-style-type: none"> <li>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></li> </ul>	<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"> <li>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.</li> </ul>	<input type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>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.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> 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).</li> </ul>	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> 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></li> </ul>	<input 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>
---	--

**CONTENTS OF ACTION PACKAGE**

❖ Copy of this Action Package Checklist <sup>4</sup>	Yes
<b>Officer/Employee List</b>	
❖ 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
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) Approval; February 7, 2012
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	April 7, 2012
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	NDA 022408 Natroba (spinosad) Topical Suspension, 0.9%; NDA 022129 Ulesfia (benzl alcohol) Lotion

<sup>4</sup> Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> <li>❖ 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>)</li> </ul>	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	April 7, 2012
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	NDA 022408 Natroba (spinosad) Topical Suspension, 0.9%; NDA 022129 Ulesfia (benzyl alcohol) Lotion
<ul style="list-style-type: none"> <li>❖ Labels (<b>full color</b> carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	February 3, 2012
<ul style="list-style-type: none"> <li>❖ Proprietary Name               <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> <li>• Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</li> </ul> </li> </ul>	November 17, 2011 Proprietary Name Request Conditionally Acceptable Letter; October 28, 2011 Proprietary Name Review
<ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA 10/14/2011 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) 12/2/2011 <input checked="" type="checkbox"/> ODPD (DDMAC) 12/5/2011 <input checked="" type="checkbox"/> SEALD 2/1/2012 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<b>Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>❖ Administrative Reviews (<i>e.g., RPM Filing Review<sup>5</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> </ul>	6/7/2011
<ul style="list-style-type: none"> <li>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</li> <li>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</li> </ul>	<input checked="" type="checkbox"/> Not a (b)(2) <input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP               <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action

<sup>5</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>12/7/2011</u> If PeRC review not necessary, explain: _____</li> <li>• Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
❖ 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
❖ Outgoing communications ( <i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i> )	1/18/2012- Transfer of Ownership 10/27/2011- Information Request 9/23/2011- Information Request 9/15/2011- Information Request 8/26/2011- Information Request 8/25/2011- Information Request 8/24/2011- Information Request 7/29/2011- Information Request 7/22/2011- Information Request 6/16/2011- Information Request 6/8/2011- Filing Issues Identified 5/27/2011- Information Request 5/11/2011- Information Request 4/14/2011- Acknowledge NDA
❖ Internal memoranda, telecons, etc.	9/20/2011
❖ 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 type="checkbox"/> No mtg January 12, 2011
• EOP2 meeting ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> No mtg August 12, 2009
• Other milestone meetings (e.g., EOP2a, CMC pilots) ( <i>indicate dates of mtgs</i> )	January 8, 2011 SPA Meeting November 14, 2008 Guidance Meeting July 24, 2006 Pre-IND Meeting
❖ 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> )	
<b>Decisional and Summary Memos</b>	
❖ 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 February 6, 2012
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None February 2, 2012
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input type="checkbox"/> None
<b>Clinical Information<sup>6</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	See CDTL review dated 2/2/2012

<sup>6</sup> Filing reviews should be filed with the discipline reviews.

<ul style="list-style-type: none"> <li>Clinical review(s) <i>(indicate date for each review)</i></li> </ul>	January 5, 2012
<ul style="list-style-type: none"> <li>Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i></li> </ul>	<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 type="checkbox"/> and include a review/memo explaining why not <i>(indicate date of review/memo)</i>	Page 19, of 1/5/2012 Clinical Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>	<input type="checkbox"/> None 11/8/2011 PMHS Addendum; 10/24/2011 PMHS Addendum; 8/29/2011 PMHS Review; 7/19/2011 PMHS Review
❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and Supporting Statement <i>(indicate date(s) of submission(s))</i></li> <li>REMS Memo(s) and letter(s) <i>(indicate date(s))</i></li> <li>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></li> </ul>	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) <i>(include copies of DSI letters to investigators)</i>	<input type="checkbox"/> None requested 11/14/2011 Clinical Inspection Summary; 11/10/2011 NAI Letter; 11/9/2011 NAI Letters (2); 10/29/2011 NAI Letter
<b>Clinical Microbiology</b> <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
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Statistical Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 11/23/2011
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 11/22/2011; 6/1/2011 Filing Review
❖ DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of DSI letters)</i>	<input checked="" type="checkbox"/> None

<b>Nonclinical</b> <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 2/2/2012 Addendum; 11/16/2011; 5/27/2011 Filing Review
❖ 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
<b>Product Quality</b> <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 checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 2/3/2012 Addendum; 11/17/2011; 5/26/2011 Filing Review
❖ Microbiology Reviews <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 (OMPQ/MAPCB/BMT) ( <i>indicate date of each review</i> )	<input type="checkbox"/> Not needed 9/14/2011; 8/24/2011
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer ( <i>indicate date of each review</i> )	<input checked="" 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> )	Page 53, 11/17/2011 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 sites<sup>7</sup></i> )	Date completed: 2/3/2012 <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

<sup>7</sup> 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.

❖ NDAs: Methods Validation (*check box only, do not include documents*)

- Completed
- Requested
- Not yet requested
- Not needed (per review)

## 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.

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

/s/  
-----

DAWN WILLIAMS  
02/07/2012

**From:** Williams, Dawn  
**Sent:** Friday, February 03, 2012 12:45 PM  
**To:** 'Lisa.Deluca@sanofipasteur.com'  
**Cc:** Gould, Barbara  
**Subject:** FDA Proposal FPI NDA 202736 Sklice (ivermectin) Lotion, 0.5%



FDA Proposal FPI  
NDA 202736 Sk...

Hello Lisa-

Please see our most recent labeling proposal as discussed during our 12:30pm teleconference. As stated, you will be providing your response to this proposal by Monday morning, February 6, 2012. Thank you!

LCDR Dawn Williams, B.S.N., U.S.P.H.S.  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research  
10903 New Hampshire Ave.  
Silver Spring, MD 20993  
Tel. 301-796-5376  
Fax 301-796-9895  
email: dawn.williams@fda.hhs.gov

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

/s/  
-----

DAWN WILLIAMS  
02/03/2012

**From:** Williams, Dawn  
**Sent:** Thursday, January 26, 2012 11:55 AM  
**To:** 'Lisa.Deluca@sanofipasteur.com'  
**Cc:** Gould, Barbara  
**Subject:** FDA Labeling Proposal NDA 202736 Sklice (ivermectin) Lotion, 0.5%



FDA Proposal PPI  
Sklice (iverm...



FDA Proposal FPI  
NDA 202736 Sk...

Hi Lisa-

Please see our most recent labeling proposal for NDA 202736 Sklice (ivermectin) Lotion, 0.5%. Note that the only additional revision from yesterday's proposal is the removal of (b) (4) in the HIGHLIGHTS section and the Indication section of the PI. Similarly, we have revised the language on the PPI also. We are still requesting your response to this proposal by noon, Friday, January 27, 2012. Thank you!

LCDR Dawn Williams, B.S.N., U.S.P.H.S.  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research  
10903 New Hampshire Ave.  
Silver Spring, MD 20993  
Tel. 301-796-5376  
Fax 301-796-9895  
email: dawn.williams@fda.hhs.gov

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

/s/  
-----

DAWN WILLIAMS  
01/26/2012

**From:** Williams, Dawn  
**Sent:** Wednesday, January 25, 2012 6:58 AM  
**To:** 'Lisa.Deluca@sanofipasteur.com'  
**Cc:** Gould, Barbara  
**Subject:** FDA Labeling Proposal NDA 202736 Sklice (ivermectin) Lotion, 0.5%



FDA Proposal PPI  
Sklice (iverm...



FDA Proposal FPI  
NDA 202736 Sk...



FDA Proposal FPI  
NDA 202736 Sk...

Good Morning Lisa-

Attached are our most recent proposals for both the FPI and PPI for your pending application for NDA 202736 Sklice (ivermectin) Lotion, 0.5%. The FPI has been provided in both redline and clean versions, while the PPI is provided in a redline version only. We have one further revision for the carton and container labels below. Please provide your response to this proposal by noon Friday, January 27, 2012. Thank you!

Carton and Container label comment:

The weight of your product should be expressed as the following: "Net wt 4 oz. (117 g)"  
It is currently expressed as the following: "4 oz. (117 g)"

LCDR Dawn Williams, B.S.N., U.S.P.H.S.  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research  
10903 New Hampshire Ave.  
Silver Spring, MD 20993  
Tel. 301-796-5376  
Fax 301-796-9895  
email: dawn.williams@fda.hhs.gov

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

/s/  
-----

DAWN WILLIAMS  
01/25/2012



NDA 202736

**ACKNOWLEDGE TRANSFER NDA OWNERSHIP**

Sanofi-Topaz, Inc.  
Attention: Lisa DeLuca, Ph.D.  
Vice President, Regulatory Affairs and Quality Assurance  
100 Witmer Road (Suite 280)  
Horsham, PA 19044

Dear Dr. DeLuca:

We acknowledge the December 14, 2011, receipt of your correspondence notifying the Food and Drug Administration of the change of ownership of the following new drug application (NDA):

Name of Drug Product: Sklice (ivermectin) Lotion, 0.5%

NDA Number: 202736

Name of New Applicant: Sanofi-Topaz, Inc.

Name of Previous Applicant: Topaz Pharmaceuticals, Inc.

Your correspondence provided the information necessary to effect this change, and we have revised our records to indicate Sanofi-Topaz, Inc. as the applicant of record for this application.

**DRUG MASTER FILE LOA**

If your NDA references any Drug Master Files (DMF), we request that you notify your suppliers and contractors who have DMFs referenced by your NDA of the change so that they can submit a new letter of authorization (LOA) to their Drug Master File(s) and send you a copy of the new LOAs. Please submit these copies of the LOAs to this NDA.

**REPORTING REQUIREMENTS**

All changes to the information in the NDA from that described by the original owner, such as manufacturing facilities and controls, must be reported to us prior to implementation. However, changes in the name of the manufacturer, packer, or distributor in the drug product's label or labeling may be reported in the next annual report. Refer to the *Guidance for Industry: Changes to an Approved NDA or ANDA* for information on reporting requirements. We request that you notify your suppliers and contractors who have DMFs referenced by your application of the change in ownership so that they can submit a new LOA to their DMFs.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 21 CFR 314.81. In addition, you are responsible for any correspondence outstanding as of the effective date of the transfer.

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 Dermatology and Dental Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If you have any questions, call me, at (301) 796-5376.

Sincerely,

*{See appended electronic signature page}*

Dawn Williams, B.S.N.  
Regulatory Health Project Manager  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

CC: Topaz Pharmaceuticals, Inc.

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

/s/  
-----

DAWN WILLIAMS  
01/18/2012

**From:** Williams, Dawn  
**Sent:** Wednesday, January 11, 2012 7:10 AM  
**To:** 'Lisa DeLuca'  
**Cc:** Gould, Barbara  
**Subject:** NDA 202736 Sklice (ivermectin) Lotion, 0.5% FDA Labeling Proposal



NDA 202736  
KLICE (ivermectin).

Good Morning Lisa-

Attached is the FDA proposed FPI. We will be sending the PPI at a later date. The FDA proposal for the carton and container labels are below. Please provide your response to our labeling proposal by close of business January 25, 2012. If you have any questions regarding our proposal, please do not hesitate to contact me at the phone number listed below in my signature block. Thank you!

Container Label:

1. Remove (b) (4)
2. The dosage strength should be expressed as the following "Lotion, 0.5%" - a comma needs to be added between the word "Lotion" and the strength
3. The net contents should be adjusted to (b) (4)
4. Include the route of administration on the back panel of the container label. As currently presented, the statement "For topical use on the scalp hair and scalp only" does not appear on the back panel. This statement may appear under the product dosage form and strength (Lotion, 0.5%).
5. Relocate the warning statement "For single use. Discard the tube after use." Further up on the principal display panel, and closer to the other warning statement "for topical use on the scalp hair and scalp only". As currently presented, the warning statement "For single use. Discard the tube after use." lack prominence.

Carton Label:

1. Remove (b) (4)
2. The dosage strength should be expressed as the following "Lotion, 0.5%" - a comma needs to be added between the word "Lotion" and the strength
3. The weight should be adjusted to (b) (4)
4. Include the warning statement "For single use. Discard the tube after use." On the principal display panel of the carton labeling. As currently presented, this statement appears only on the top and bottom closure flaps and lacks prominence.
5. Relocate the "Rx Only" statement to the bottom portion of the back panel of the carton labeling. Additionally, unbold the "Rx Only" statement. As currently presented, "Rx Only" is placed in close proximity to the route of administration statement and distracts from the important warning statement, "For topical use on the scalp hair and scalp only".
6. Delete the company name (b) (4) on the back panel of the carton labeling. As currently presented, the name (b) (4) is too prominent and distracts from the product quantity statement. Additionally, the company name appears on the principal display panel.
7. Increase the prominence of the route of administration statement on the back panel of the carton labeling by bolding the statement. As currently presented, the statement "For topical use on the scalp hair and scalp only" lack prominence.
8. Include the route of administration statement on the side panels of the carton labeling. As currently presented, the statement "For topical use on the scalp hair and scalp only" does not appear on the side panels. The statement may appear under the product dosage form and strength (Lotion, 0.5%).

Carton and Container Labeling:

1. Delete the graphic presentation next to the proprietary name. As currently presented, the graphic can distract from the proprietary name, the established name, and the product strength.
2. Increase the font size of the dosage form and the strength statements (Lotion, 0.5%) that appear under the established name on the principal display panels, side panels, or the back panels of the container label and the carton labeling, to appear the same size as the established name. Additionally, relocate the strength statement, 0.5% to immediately under the dosage form. Increasing the font size of the dosage form and the strength statements will provide more prominence to these statements.
3. Delete the multi-color graphic on the container label and the carton labeling. The multi-color graphic, especially the purple portion of the graphic design can distract from other important information such as the product name, the route of administration, and the warning statements.
4. Relocate the "Rx Only" statement to the bottom portion of the principal display panel of both the container label and the carton labeling. Additionally, unbold the "Rx Only" statement. As currently presented, "Rx Only" is placed in close proximity to the route of administration statement and distracts from the important warning statement. "For Topical use on the scalp hair and scalp only".
5. Increase the prominence of the route of administration statement by bolding the statement. Additionally, move the route of administration statement up, and closer to the dosage form and strength statements. As currently presented, the statement "For topical use on the scalp hair and scalp only" lack prominence.
6. Relocate the company name, (b) (4) from the top portion of the principal display panel of both the container label and the carton labeling to the bottom portion of the principal display panel, and decrease the font size of (b) (4). As currently presented, the name (b) (4) is too prominent and too close to the proprietary name, and may be misinterpreted as the proprietary name.
7. Relocate the warning statements "Keep out of reach of children. Use in children should be under the direct supervision of an adult. Avoid eye contact." To the principal display panel of the carton labeling and the front of the container label. Relocating the important warning statements provides more prominence to the statements.

LCDR Dawn Williams, B.S.N., U.S.P.H.S.  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research  
10903 New Hampshire Ave.  
Silver Spring, MD 20993  
Tel. 301-796-5376  
Fax 301-796-9895  
email: dawn.williams@fda.hhs.gov

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

/s/  
-----

DAWN WILLIAMS  
01/11/2012



NDA 202736

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Topaz Pharmaceuticals Inc  
100 Witmer Road, Suite 280  
Horsham, PA 19044

ATTENTION: Lisa DeLuca, PhD  
Vice President, Regulatory Affairs and Quality Assurance

Dear Dr. DeLuca:

Please refer to your New Drug Application (NDA) dated April 7, 2011, received April 7, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ivermectin Lotion, 0.5%.

We also refer to your August 23, 2011, correspondence, received August 23, 2011, requesting review of your proposed proprietary name, Sklice. We have completed our review of the proposed proprietary name, Sklice and have concluded that it is acceptable.

The proposed proprietary name, Sklice, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your August 23, 2011 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet Anderson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0675. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Dawn Williams at (301) 796-5376.

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

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

/s/  
-----

CAROL A HOLQUIST  
11/17/2011



NDA 202736

**INFORMATION REQUEST**

Topaz Pharmaceuticals  
Attention: Lisa DeLuca, Ph.D.  
Vice President, Regulatory Affairs and Quality Assurance  
100 Witmer Road, Suite 280  
Horsham, PA 19044

Dear Dr. DeLuca:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sklice (ivermectin) Cream, 0.5%.

We are reviewing the Chemistry, Manufacturing and Controls (CMC) sections of your submission. Please refer to the informal response and the R&D sample (viscosity of (b) (4) provided by Topaz Pharmaceuticals on October 5, 2011. Please also refer to the response provided by Topaz Pharmaceuticals on October 11, 2011, indicating that Topaz agrees to the dosage form of lotion.

We request your prompt written response to the following information request by November 2, 2011:

The R&D sample provided with a viscosity of (b) (4) cPs appears to be (b) (4) (b) (4) and therefore not a lotion. Because you agree that the commercial product dosage form is a lotion, an upper end limit of (b) (4) cPs for the viscosity acceptance criterion is not acceptable. Amend the specification table in Module 3 Section 3.2.P.5.1 by establishing an acceptance criterion of 8,000-30,000 cPs for the viscosity test. Amend relevant sections of Module 3 for the revised viscosity acceptance criterion.

To facilitate prompt review of your response, please also provide an electronic courtesy copy of your response to both Jeannie David, Regulatory Project Manager in the Office of New Drug Quality Assessment (Jeannie.David@fda.hhs.gov), and Dawn Williams, Regulatory Project Manager the Office of New Drugs (Dawn.Williams@fda.hhs.gov).

If you have any questions regarding this CMC letter, please contact Jeannie David, Regulatory Project Manager, at (301) 796-4247.

Sincerely,

*{See appended electronic signature page}*

Moo-Jhong Rhee, Ph.D.  
Chief, Branch IV  
Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment  
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/  
-----

MOO JHONG RHEE  
10/27/2011  
Chief, Branch IV



NDA 202736

**INFORMATION REQUEST**

Topaz Pharmaceuticals  
Attention: Lisa DeLuca, Ph.D.  
Vice President, Regulatory Affairs and Quality Assurance  
100 Witmer Road, Suite 280  
Horsham, PA 19044

Dear Dr. DeLuca:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sklice (ivermectin) Cream, 0.5%.

We are reviewing the Chemistry, Manufacturing and Controls (CMC) sections of your submission. Please also refer to the teleconference held between Topaz Pharmaceuticals and the FDA on August 19, 2011, our Information Request letter dated August 24, 2011, your amendment dated September 6, 2011, and the teleconference held September 20, 2011. We are providing our official information requests for remaining outstanding issues. We request your written responses no later than October 14, 2011.

- 1) Officially amend the method (73.6860) in the NDA as discussed in your response dated September 6, 2011.
- 2) We recommend that lotion be the dosage form for the proposed product (b) (4)  
Provide a statement to indicate your acceptance of the recommendation, and revise all proposed labels and labeling to indicate that lotion is the dosage form.
- 3) Lower the upper limit of the acceptance criterion for viscosity to a value which can be supported by the release and stability data.
- 4) To support the proposed viscosity acceptance criterion, provide a sample of the proposed product whose viscosity is near the proposed upper limit. The sample can come from a R&D batch.

To facilitate prompt review of your response, please also provide an electronic courtesy copy of your response to both Jeannie David, Regulatory Project Manager in the Office of New Drug Quality Assessment (Jeannie.David@fda.hhs.gov), and Dawn Williams, Regulatory Project Manager the Office of New Drugs (Dawn.Williams@fda.hhs.gov).

If you have any questions regarding this CMC letter, please contact Jeannie David, Regulatory Project Manager, at (301) 796-4247.

Sincerely,

*{See appended electronic signature page}*

Moo-Jhong Rhee, Ph.D.  
Chief, Branch IV  
Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment  
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/  
-----

MOO JHONG RHEE  
09/23/2011  
Chief, Branch IV



**MEMORANDUM OF MEETING MINUTES**

**TYPE OF MEETING:** FDA-initiated and scheduled CMC teleconference  
**MEETING DATE:** September 20, 2011  
**TIME:** 1:00 – 1:30 PM EST  
**APPLICATION:** NDA 202-736  
**DRUG NAME:** Sklice (ivermectin) Cream, 0.05%  
**SPONSOR:** Topaz Pharmaceuticals  
**PHONE NUMBER CALLED:** Dial-in numbers provided by Topaz Pharmaceuticals  
**MEETING CHAIR:** Caroline Strasinger, Ph.D.  
**MEETING RECORDER:** Jeannie David, M.S.

**FDA PARTICIPANTS:**

*FDA/CDER/OPS/Office of New Drug Quality Assessment (ONDQA)*

Carline Strasinger, Ph.D., Review Chemist  
Shulin Ding, Ph.D., CMC Lead  
Jeannie David, M.S., Regulatory Health Project Manager

*FDA/CDER/ODEIII/Division of Dermatology and Dental Products*

Jane Liedtka, M.D., Clinical Reviewer  
Jill Lindstrom, M.D., Clinical Team Leader

**EXTERNAL PARTICIPANTS:**

*Topaz Pharmaceuticals*

Lisa DeLuca, Vice President Regulatory Affairs and Quality Assurance  
Tom Beck, Chief Medical Officer  
Bill Ryan, Vice President Clinical and Medical Affairs  
Bob Verdugo, Vice President Operations

*DPT Laboratories, Ltd.*

Kay Mary Harrell, Senior Director, CMC Regulatory Affairs

[Redacted] (b) (6)

[Redacted] (b) (6)

**BACKGROUND:**

The applicant submitted new NDA 202-736 dated April 7, 2011, to the Division of Dermatology and Dental Products for Sklice (ivermectin) Cream, 0.05% for the treatment of head lice (b) (4) in patients 6 months of age and older. An Agency-requested CMC teleconference was held on August 19, 2011, and a follow up Information Request letter was sent on August 24, 2011. The applicant submitted their responses to the information requests on September 6, 2011. After review of the responses, a CMC teleconference was requested on September 19, 2011, to occur on September 20, 2011. The following points were sent by email to Topaz Pharmaceuticals on September 19, 2011, in preparation for the September 20, 2011, teleconference:

- 1) Officially amending the method (73.6860) in the NDA as discussed in your response provided 6-SEP-2011.

- 2) Clarifying the retention time of (b) (4). In the introduction to method 73.6727 the retention time is said to be (b) (4) however all chromatograms indicate that the impurity has an RRT of (b) (4).
- 3) Discussing the dosage form (cream versus lotion).
- 4) Lowering the acceptance criterion for viscosity to a value supported by release and stability data.

**POINTS DISCUSSED:**

- 1) Officially amending the method (73.6860) in the NDA as discussed in your response provided 6-SEP-2011.
  - FDA stated that to adhere to GRMP timeline given to discipline reviews , CMC amendments submitted later than October 14, 2011 may not be reviewed
  - Topaz agreed to the timeline of Oct. 14, 2011 for official submission of amended method 73.6860.
  - Topaz also stated that they plan to provide a draft in advance of the final submission, in 10 days – 2 weeks, and highlight any changes between the draft and final submission when the final submission is submitted.
- 2) Clarifying the retention time of (b) (4). In the introduction to method 73.6727 the retention time is said to be (b) (4) however all chromatograms indicate that the impurity has an RRT of (b) (4).
  - Topaz clarified that the (b) (4) value given in the introduction to method 73.6727 is the *relative* retention time, which corresponds to a retention time of (b) (4) considering that the retention time of ivermectin peak is (b) (4).
- 3) Discussing the dosage form ( (b) (4) versus lotion).
  - FDA stated that the Agency believes that lotion would be more appropriate than the currently proposed cream dosage form. Based on the samples given, the product does not appear to meet the USP definition for a cream. USP<1151> Pharmaceutical Dosage Forms defines creams as semisolid dosage forms. Semisolids are preparations that do not flow They maintain their shape upon dispensing. The proposed product flows and does not maintain shape; therefore, it should be a liquid (lotion) rather than a semisolid (cream). If a cream designation were granted, this product would not align with other cream products approved by the Agency.
  - Topaz requested time to discuss with their management, and asked what would be needed to close this issue out if they were to agree with the Agency.
  - FDA stated that they would need to provide a formal statement to NDA 202-736 to indicate the agreement to change the dosage form from cream to lotion, and submit revisions to all labels and labeling accordingly.
  - Topaz agreed to officially respond in 10 days.
- 4) Lowering the acceptance criterion for viscosity to a value supported by release and stability data.
  - FDA noted in reviewing the stability and batch release data, that the values do not approach the proposed upper limit of the acceptance criterion for viscosity.
  - Topaz agreed to submit an amendment in 10 days to propose a suitable acceptance criterion for viscosity.

**ACTION ITEMS FOR SPONSOR:**

1. Submit the revised method (73.6860) no later than October 14, 2011. Provide an informal draft of this submission within 10 days-2 weeks (by October 4), 2011.
2. Submit an amendment in 10 days to officially respond to the deficiencies regarding dosage form and viscosity acceptance criterion.

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

/s/  
-----

JEANNIE C DAVID  
09/23/2011

CAROLINE STRASINGER  
09/23/2011

MOO JHONG RHEE  
09/23/2011  
Chief, Branch IV



NDA 202736

## INFORMATION REQUEST

CERTIFIED MAIL  
RETURN RECEIPT REQUESTED

Topaz Pharmaceuticals  
Attention: Lisa DeLuca, PhD  
Vice President, Regulatory Affairs and Quality Assurance  
100 Witmer Road, Suite 280  
Horsham, PA 19044

Dear Dr. DeLuca:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sklice (ivermectin) Cream, 0.5%.

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).<sup>1</sup> 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

---

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

searching available documentation to determine which NDAs are impacted by the above findings.

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 Barbara Gould, Chief, Project Staff Management, at (301) 796-4224.

Sincerely,

*{See appended electronic signature page}*

Susan J. Walker, M.D., F.A.A.D.  
Director  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
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/  
-----

BARBARA J GOULD

09/15/2011

p.p. DIVISION DIRECTOR Susan J. Walker



NDA 202736

**INFORMATION REQUEST**

Topaz Pharmaceuticals  
Attention: Lisa DeLuca, PhD  
Vice President, Regulatory Affairs and Quality Assurance  
100 Witmer Road, Suite 280  
Horsham, PA 19044

Dear Dr. DeLuca:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sklice (ivermectin) Cream, 0.5% for the topical treatment of head lice <sup>(b) (4)</sup> in patients 6 months of age and older.

We also refer to your July 1, 2011 submission, containing revised labeling.

We are reviewing the Pharmacology/Toxicology section of your submission and have the following comments and information requests. We request a prompt written response by August 26, 2011 in order to continue our evaluation of your NDA.

Provide the calculation method used for the animal multiple of human exposure values provided in Section 8.1 of the label submitted on July 1, 2011.

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

Sincerely,

*{See appended electronic signature page}*

Jill Lindstrom, M.D.  
Clinical Team Leader  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
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/  
-----

JILL A LINDSTROM  
08/26/2011



NDA 202736

**INFORMATION REQUEST**

Topaz Pharmaceuticals  
Attention: Lisa DeLuca, Ph.D.  
Vice President, Regulatory Affairs and Quality Assurance  
100 Witmer Road, Suite 280  
Horsham, PA 19044

Dear Dr. DeLuca:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sklice (ivermectin) Cream, 0.5%.

We are reviewing the Chemistry, Manufacturing and Controls (CMC) sections of your submission. We request your prompt written response to these information requests in order to continue our evaluation of your NDA.

- 1) The bulk drug substance will not support growth at [REDACTED] (b) (4) but it may contain spores. Was this issue addressed in the failure investigation? Is there a relationship between the bulk drug substance lots and the contaminated product? An ICH Q6a assessment of the ingredients should be implemented and reported.
- 2) Include a microbial limits test in the finished product specifications. Provide assurance that the standard test will detect the [REDACTED] (b) (4) strain in question sufficiently.
- 3) The fact that a drop in preservative content was not seen implies that the [REDACTED] (b) (4) strain isolated is not affected by the preservative. In this case, a specific testing program should be implemented to detect and eliminate this organism from the manufacturing environment. How will contamination with this specific organism be avoided in the future?
- 4) Justify the drop in minimum preservative requirements from [REDACTED] (b) (4) in the stability protocol. Will the product with [REDACTED] (b) (4) of its preservatives pass the antimicrobial effectiveness test (USP<51>)?

To facilitate prompt review of your response, please also provide an electronic courtesy copy of your response to both Jeannie David, Regulatory Project Manager in the Office of New Drug Quality Assessment (Jeannie.David@fda.hhs.gov), and Dawn Williams, Regulatory Project Manager the Office of New Drugs (Dawn.Williams@fda.hhs.gov).

If you have any questions regarding this CMC letter, please contact Jeannie David, Regulatory Project Manager, at (301) 796-4247.

Sincerely,

*{See appended electronic signature page}*

Moo-Jhong Rhee, Ph.D.  
Chief, Branch IV  
Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment  
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/  
-----

MOO JHONG RHEE  
08/25/2011  
Chief, Branch IV



NDA 202736

**INFORMATION REQUEST**

Topaz Pharmaceuticals  
Attention: Lisa DeLuca, Ph.D.  
Vice President, Regulatory Affairs and Quality Assurance  
100 Witmer Road, Suite 280  
Horsham, PA 19044

Dear Dr. DeLuca:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sklice (ivermectin) Cream, 0.5%.

We are reviewing the Chemistry, Manufacturing and Controls (CMC) sections of your submission. Please also refer to the teleconference held between Topaz Pharmaceuticals and the FDA on August 19, 2011. As stated in the August 19, 2011, teleconference, we are providing our official comments and information requests in this follow-up letter to reflect our understanding from the teleconference discussion. We request your prompt written response to these information requests by September 2, 2011.

- 1) DMFs (b) (4) and (b) (4) have administrative filing issues and therefore are unable to be reviewed for NDA 202-736 at this time. All DMFs must be adequate to support NDA 202-736 prior to approval.
- 2) Although (b) (4) has provided a Certificate of Suitability (CSE) from EDQM, provide a BSE statement for (b) (4) Crodalan AWS.
- 3) Regarding the described in-process control procedures conducted during the filling operation, provide more information on Inspection by Attributes, specifically how inspection for contaminated or defective product is conducted.
- 4) Regarding the analytical procedure to measure pH (b) (4) provide additional information discussing the (b) (4). More specifically, the referenced USP monograph does not apply as there is no procedure for measuring pH and the monograph calls for (b) (4).
- 5) Regarding Characterization of Impurities, the described Lot BEF at 18 months and 25°C/60%RH was stated to have a peak exceeding (b) (4) area of label claim at an RRT of (b) (4). The RRT of (b) (4) could not be located in the stability data nor a peak exceeding (b) (4) area for Lot BEF at 18 months. Clarify and/or provide information regarding this issue.

- 6) Regarding the analytical procedure for ID, Assay, Degradation Products (73.6860), clarify if “%w/w Ivermectin” in the following equation should be “%w/w Impurity”, and also provide the value used for the term “Label Claim”.

$$\%L \text{ Impurity} = \frac{\%w/w \text{ Ivermectin}}{\text{Label Claim}} \times 100$$

- 7) Describe how RRF, used in the following equation, is calculated (if RRF is the ratio of the optical response of an impurity to that of the standard, we believe that the RRF should be in the denominator of the equation) and provide the values of RRF for the impurities. Additionally, verify that the equation below as written is correct (we also believe that the whole equation should be multiplied by 100 to get a % value).

$$\%w/w \text{ impurity} = \frac{Ru_i \times W_{std} \times P \times RRF \times 20}{Rs_{H_2B_{1a}} \times W_{sample}}$$

Where,

- $Ru_i$  = the area response for impurity in the sample chromatogram.  
 $Rs_{H_2B_{1a}}$  = the mean area response of Ivermectin ( $H_2B_{1a}$  only) in the working standards injected throughout the sample set  
 $W_{std}$  = the weight (g) of the USP Ivermectin reference standard  
 $P$  = the purity of the USP Ivermectin reference standard in decimal form for Ivermectin ( $H_2B_{1a}$  only)  
 $W_{sample}$  = the weight (g) of the sample  
 $20$  = dilution factor  
 $RRF$  = relative response factor of impurity (use value of 1.0 if no RRF available).

- 8) The proposed specification for Unspecified Impurities is NMT  $(b)(4)$  each. The stability data provided lists the specification as  $(b)(4)$  Area; many of the impurities are found at levels exceeding the NMT  $(b)(4)$  throughout stability testing. It is unclear if NMT  $(b)(4)$  is equal to NMT  $(b)(4)$  Area. Additionally, the “Attribute” titles do not reflect the “Test” title making it difficult to review the stability data.
- Provide information describing the relationship between %L and %area. Provide the equations for both %L and %area..
  - Provide a table indicating what each test on the proposed shelf-life specification corresponds to in the provided stability data.
  - Convert related substances stability data expressed as % Area into %L.
  - Provide a comparative table of stability data using previous method (73.6416) and the proposed regulatory method (73.6860) on assay and on unspecified impurities to demonstrate the proposed regulatory method is at least equivalent, if not superior, to the previous method.

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

/s/  
-----

MOO JHONG RHEE  
08/24/2011  
Chief, Branch IV



NDA 202736

## INFORMATION REQUEST

Topaz Pharmaceuticals  
Attention: Lisa DeLuca, PhD  
Vice President, Regulatory Affairs and Quality Assurance  
100 Witmer Road, Suite 280  
Horsham, PA 19044

Dear Dr. DeLuca:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sklice (ivermectin) Cream, 0.5% for the topical treatment of head lice <sup>(b) (4)</sup> in patients 6 months of age and older.

We are reviewing the clinical section of your submission and have the following comments and information requests. We request a prompt written response by August 12, 2011, in order to continue our evaluation of your NDA.

1. Revise the safety population to exclude the subjects in the dermal safety study TOP007 since these subjects were not “treated” with the investigational product in the manner used for the pivotal studies. This means the safety population will consist of subjects treated with topical Ivermectin Cream 0.5% from Studies TOP011, TOP012, TOP010, TOP001 (excluding oral Ivermectin subjects), TOP003 (excluding subjects who received 0.15% and 0.25% Ivermectin). Subjects from these studies will be included if they were randomized and dispensed medication. Exclude subjects from TOP008 since this was an open-label study.

For this “revised safety population” provide the following:

- New demographic tables including information on gender, age (Including subgroups 0.5-2 yrs, 2-4 yrs, 4-12 yrs, 12-16 yrs, >16 yrs) ethnicity, race and weight
- New disposition tables with reasons specified
- New presentation of Common Adverse Events (AEs) with tables for incidence and by Body System and preferred terms (i.e. replace Table 2.1 from Section 5.3.5.3.1 of ISS and Table 2.2 from Section 5.3.5.3.1 of ISS). Include information on AEs occurring at a rate of 1% or greater in the treated group and for which the rate for drug exceeds the rate for placebo)
- New subgroup analysis by age group, gender and race

2. Provide follow-up on subject #TOP010-03-108-05 who experienced a severe adverse event (conjunctivitis) that was ongoing at study completion.
3. Provide age demographics divided into the following age groups for Study TOP010: 0.5-2 yrs, 2-4 yrs, 4-12 yrs, 12-16 yrs, >16 yrs.

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

Sincerely,

*{See appended electronic signature page}*

Jill Lindstrom, MD  
Clinical Team Leader  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
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/  
-----

JILL A LINDSTROM  
07/29/2011



NDA 202736

**INFORMATION REQUEST**

Topaz Pharmaceuticals  
Attention: Lisa DeLuca, PhD  
Vice President, Regulatory Affairs and Quality Assurance  
100 Witmer Road, Suite 280  
Horsham, PA 19044

Dear Dr. DeLuca:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sklice (ivermectin) Cream, 0.5% for the topical treatment of head lice <sup>(b) (4)</sup> in patients 6 months of age and older.

We are reviewing the Clinical Studies section of your submission and have the following comments and information requests. We request a prompt written response by close of business, Friday, July 22, 2011 in order to continue our evaluation of your NDA.

For Study TOP008, provide information regarding number of lice identified at enrollment in each subject.

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

Sincerely,

*{See appended electronic signature page}*

Jill Lindstrom, MD  
Clinical Team Leader  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
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/  
-----

JILL A LINDSTROM  
07/22/2011



NDA 202736

**INFORMATION REQUEST**

Topaz Pharmaceuticals  
Attention: Lisa DeLuca, PhD  
Vice President, Regulatory Affairs and Quality Assurance  
100 Witmer Road, Suite 280  
Horsham, PA 19044

Dear Dr. DeLuca:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sklice (ivermectin) Cream, 0.5% for the topical treatment of head lice <sup>(b) (4)</sup> in patients 6 months of age and older.

We are reviewing the clinical studies section of your submission and have the following information request. We request a prompt written response in order to continue our evaluation of your NDA.

Provide the calculation of the absolute neutrophil count for each subject in study TOP008 at each of the available time points, (i.e. baseline/Day 1, Day 2, Day 8 and Day 15).

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

Sincerely,

*{See appended electronic signature page}*

Jill Lindstrom, M.D.  
Clinical Team Leader  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
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/  
-----

JILL A LINDSTROM  
06/16/2011



NDA 202736

**FILING COMMUNICATION**

Topaz Pharmaceuticals  
Attention: Lisa DeLuca, PhD  
Vice President, Regulatory Affairs and Quality Assurance  
100 Witmer Road, Suite 280  
Horsham, PA 19044

Dear Dr. DeLuca:

Please refer to your New Drug Application (NDA) dated and received April 7, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Sklice (ivermectin) Cream, 0.5% for the topical treatment of head lice (b) (4) in patients 6 months of age and older.

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 February 7, 2012.

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 January 14, 2012.

During our filing review of your application, we identified the following potential review issues:

**Chemistry, Manufacturing, and Controls (CMC)**

1. Provide drug product samples, container/carton labels, and three months of stability data from at least two more batches at a scale (b) (4) of the production scale for the product packaged in the to-be-marketed tube system supplied by (b) (4)

2. Provide a clear rationale to support the method changes from Method 73.6416 to improved Method 73.6416, and then to the proposed regulatory method 73.6860. Provide a comparison among the three methods regarding procedures, chromatographic conditions, method precision, accuracy, specificity, quantitation limit, detection limit, etc. for the assay of the active ingredient and quantitation of impurities/degradants.

### **Clinical Pharmacology/Biopharmaceutics**

3. Trial TOP001 was initiated on June 14, 2007 and the PK samples were analyzed using HPLC with tandem mass spectrometry (Bioanalytical and method identification and revision number – PSMET# AS0006) (LLOQ 5 ng/mL). The long term stability was established at -70°C for 92 days. Further, it appears that you have re-analyzed the PK samples from this trial using (a more sensitive assay) HPLC coupled with fluorescence detection (Study Identification: A092661) (LLOQ 50 pg/mL) between August 03-06, 2009.

We also notice that with trial TOP008, you have re-established the long term stability using HPLC coupled with fluorescence detection at -80°C and at -20°C for 148 days and 112 days respectively.

The available long term stability data does not provide adequate stability information to support the stability of PK samples from trial TOP001 at time of reanalysis in August 2009. Provide adequate long term stability data to support the storage stability to cover the period until re-analysis of PK samples for trial TOP001.

4. For trial TOP001, submit the electronic data set generated following re-analysis of PK samples using HPLC coupled with fluorescence detection (Study Identification: A092661) (LLOQ 50 pg/mL).

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.

We also request that you submit the following information:

1. Provide drug product samples (2 units) with lower viscosity for dosage form evaluation. The viscosity of the samples should be near the lower limit of the proposed viscosity acceptance criterion. The samples should be accompanied by their certificates of analysis.
2. Confirm that the tube system supplied by (b) (4) to-be-marketed container/closure systems proposed for NDA 202736 as stated in Section 3.2.P.7.
3. You have proposed (b) (4)

(b) (4)

4. It appears that the animal multiples of the maximum recommended human dose described in Sections 8.1 and 13.1 were copied from the Stromectol label. Modify these multiples because the human exposure to ivermectin is different when using your drug product and Stromectol tablet.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. Prior to the HIGHLIGHTS section of your label, you have a logo displayed with the proprietary name presentation of your product. There should be no logo displayed.
2. In the HIGHLIGHTS section of your Prescribers' Information (PI), the required section heading "WARNINGS AND PRECAUTIONS" is missing.
3. In the HIGHLIGHTS/INDICATIONS AND USAGE section of your PI, you have not proposed an established pharmacologic class. Identify the established pharmacologic class for the drug at:  
<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.
4. In the HIGHLIGHTS section of your PI, the following verbatim statement must be included, "See 17 for the Patients Counseling Information and FDA-approved patient labeling".
5. A horizontal line must separate the Table of Contents (TOC) and the Full Prescribing Information (FPI). There is not a horizontal line separating the TOC and FPI of your label.

We request that you resubmit labeling that addresses these issues by July 1, 2011. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for 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.

#### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301) 796-5376

Sincerely,

*{See appended electronic signature page}*

Susan J. Walker, M.D., F.A.A.D.  
Director  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
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/  
-----

SUSAN J WALKER  
06/08/2011



NDA 202736

**INFORMATION REQUEST**

Topaz Pharmaceuticals  
Attention: Lisa DeLuca, PhD  
Vice President, Regulatory Affairs and Quality Assurance  
100 Witmer Road, Suite 280  
Horsham, PA 19044

Dear Dr. DeLuca:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sklice (ivermectin) Cream, 0.5% for the topical treatment of head lice (b) (4) in patients 6 months of age and older.

We are reviewing the Biostatistics/Clinical section of your submission and have the following comments and information requests. We request a prompt written response by June 9, 2011 in order to continue our evaluation of your NDA.

According to the December 23, 2009 Special Protocol Agreement Letter, randomization in Phase 3 trials were planned to be stratified by site. However, in your NDA submission, you stated that “the statistician inadvertently used central randomization and not stratified randomization” for treatment allocation and that you identified the error on April 16, 2010. Consequently, you stated that you revised the randomization scheme to be stratified by site. Please clarify the following:

- how randomization was generated by the study statistician, whether any factors were used in the process of generating the randomization code, and whether computer software was used in the randomization process. Provide the program along with listing the factors (if any) over time, used in the randomization.
- the observed imbalance of treatment allocation within sites.
- how the error of the randomization scheme was discovered almost halfway through the trials, and whether the Agency was informed about this issue.

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

Sincerely,

*{See appended electronic signature page}*

Jill Lindstrom, M.D.  
Clinical Team Leader  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
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/  
-----

JILL A LINDSTROM  
05/27/2011



NDA 202736

**NDA ACKNOWLEDGMENT**

Topaz Pharmaceuticals Inc.  
Attention: Lisa DeLuca, PhD  
Vice President, Regulatory Affairs  
100 Witmer Rd., Suite 280  
Horsham, PA 19044

Dear Dr. DeLuca:

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

Name of Drug Product: Sklice<sup>®</sup> (ivermectin) Cream, 0.5%

Date of Application: April 7, 2011

Date of Receipt: April 7, 2011

Our Reference Number: NDA 202736

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 June 6, 2011, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should 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  
Division of Dermatology and Dental Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper 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/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

Sincerely,

*{See appended electronic signature page}*

Dawn Williams, BSN  
Regulatory Health Project Manager  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
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/  
-----

DAWN WILLIAMS  
04/14/2011



IND 073134

**MEETING MINUTES**

Topaz Pharmaceuticals, Inc.  
Attention: Lisa DeLuca, Ph.D.  
Vice President, Regulatory Affairs and Quality Assurance  
100 Witmer Road (Suite 280)  
Horsham, PA 19044

Dear Dr. DeLuca:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for TPZ-0434 (ivermectin) Cream, 0.5% for the topical treatment of head lice (b) (4) in patient 6 months and older.

We also refer to the teleconference scheduled on January 12, 2011, between representatives of your firm and the FDA. The purpose of the meeting was to discuss the content and format of your proposed NDA submission. Your premeeting briefing package (dated December 10, 2010) provides background and questions for discussion.

We acknowledge the email on January 11, 2011, between you and Dawn Williams, Project Manager, notifying us that after receipt and review of the premeeting communication consisting of Agency responses to your questions, you have determined that the responses to your questions are sufficient and additional discussion is not necessary.

This letter and the enclosed final responses represent the official record.

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

Sincerely,

*{See appended electronic signature page}*

Susan J. Walker, M.D., F.A.A.D.  
Director  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure – Final Responses



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

---

**FINAL RESPONSES**

**IND:** 073134

**Product:** TPZ-0434 (ivermectin) Cream, 0.5%

**Regulatory Path:** 505(b)(2)

**Listed Drug:** Stromectol<sup>®</sup> (ivermectin) Tablets

**Sponsor:** Topaz Pharmaceuticals, Inc.

**Proposed Indication:** Topical treatment of head lice (b) (4) in patients 6 months and older

**Type of Meeting:** Pre-NDA Meeting

**Meeting Date:** January 12, 2011; 9:00 AM

**MEETING OBJECTIVES:**

The objective of this meeting was to discuss the content and format of Topaz Pharmaceutical's proposed NDA submission.

**Regulatory Correspondence History**

We have had the following meetings with you:

- January 8, 2010 Post-Special Protocol Assessment Teleconference
- August 12, 2009 End of Phase 2 Meeting
- November 14, 2008 Phase 2 Dose-Ranging Guidance Meeting
- May 21, 2007 Guidance Teleconference
- July 24, 2006 Pre-IND Meeting

We have sent the following correspondences:

- July 20, 2010 Advice Letter
- May 14, 2010 Advice Letter
- December 23, 2009 Special Protocol Agreement
- August 26, 2009 Meeting Minutes
- Meeting Minutes December 22, 2008
- October 16, 2008 Advice Letter
- June 5, 2008 Advice Letter

- May 2, 2008 Advice Letter
- May 29, 2007 Advice Letter
- May 21, 2007 Advice Letter
- January 19, 2007 Advice Letter
- November 27, 2006 Advice Letter

### **Standard background information**

A 505(b)(2) application would be an acceptable approach at this time based on the information provided. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf> . In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at <http://inside.fda.gov:9003/downloads/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027521.pdf>) .

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that the regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

### **Regulatory**

#### **Question 1:**

Topaz submitted a "Proposed Pediatric Study Request" on May 10, 2010 to the IND. To date, Topaz has not received a written request from the FDA. Will the FDA provide a written request prior to the NDA submission, or will the FDA agree that studies submitted to the 0.5% Ivermectin Cream NDA before issuance of a written request will qualify for pediatric exclusivity?

**Response:**

No, a written request will not be issued by the FDA at this time. Generally, FDA's pediatric written requests will seek all necessary pediatric information for an active moiety. (b) (4)

(b) (4) Unless you wish to delay the development program for your topical ivermectin product for the indication of head lice, we do not plan to issue a pediatric written request at this time.

**Question 2:**

Topaz requests a waiver from submitting an eCTD pilot as (b) (4) is preparing the eCTD. (b) (4) filed an acceptable eCTD pilot with the Center on June 2, 2004. (b) (4) Does the FDA agree?

**Response:**

The cCTD pilot submitted by (b) (4) does not absolve Topaz Pharmaceuticals, Inc. from providing an eCTD pilot for this submission. The FDA prefers that Topaz Pharmaceuticals, Inc. arrange a test submission, prior to actual submission. Please refer to the [Submit a Sample eCTD to the FDA](#) Website for guidance on sending a test submission. You may request dataset(s) analysis for CDISC specifications compliance as part of the test submission. If requested, the Agency will provide report of the dataset(s) CDISC compliance analyses of the eCTD test submission processing to you. Please notify the Agency if you want feedback prior to your formal submission for SDTM formatted datasets submitted by sending an email to [esub@fda.hhs.gov](mailto:esub@fda.hhs.gov) or [cder-edata@fda.hhs.gov](mailto:cder-edata@fda.hhs.gov). Due to the proximity of the actual submission by Topaz Pharmaceuticals, Inc., the Agency will use this sample to provide feedback to you prior to the actual submission.

For compliance with SDTM specifications, the Agency prefers that you use as guidance the CDISC SDTM IG 3.1.2 referenced in the [Study Data Specifications](#) (pg. 4).

Additional Comment on the draft eCTD Table of Contents: - Creating additional node extensions other than what is defined in ICH and FDA specifications is not recommended nor allowed, since the information may not be properly displayed in the eCTD structure.

**Chemistry, Manufacturing and Controls (CMC)**

**Question 7:**

Will the FDA accept the NDA for filing containing 18 months of long term stability (25°C/60% relative humidity) for 3 lots (1 of which was out of specification for microbiology testing at the 6 month time point, Lot BEF), 6 months of long term stability for 1 lot, and 6 months of accelerated stability (40°C/75% relative humidity) on all 4 lots?

**Response:**

It is acceptable for filing. The NDA should include the results of the OOS investigation on the stability failure of Lot BEF.

**Question 8:**

Are Topaz' responses to the FDA EOP2 comments regarding CMC provided in the Pre-NDA meeting package adequate for the filing of the NDA (refer Table 3)?

**Response:**

They are adequate for filing with the exception of the response to End of Phase 2 meeting Question 11. The homogeneity test should be a part of drug product specification and performed for every batch. The proposed [REDACTED] (b) (4) is a review issue. You can include the proposal in the NDA for review.

Additionally, although the proposed stability update in your response to EOP2 Question 8 is permissible, the update must be received by the Agency within 24 weeks after the submission of the NDA.

**Pharmacology/Toxicology**

There were no specific Pharmacology/Toxicology questions submitted. We have the following comments:

Per the Pharmacology/Toxicology comments relayed during the End of Phase 2 meeting conducted on August 12, 2009, the nonclinical studies you have conducted appear to be adequate to support a 505(b)(2) NDA submission for your drug product if it is determined that an adequate clinical bridge has been provided between your drug product, 0.5% ivermectin cream, and Stromectol<sup>®</sup> tablets. However, additional nonclinical toxicity studies may be needed for the 0.5% ivermectin cream if the impurity profile for 0.5% ivermectin cream is significantly different than the impurity profile for Stromectol<sup>®</sup> tablets.

**Clinical Pharmacology/Biopharmaceutics**

There were no specific Clinical Pharmacology/Biopharmaceutics questions submitted. We have the following comments:

For the pharmacokinetic studies (TOP001 and TOP008), please submit the electronic datasets in the NDA submission. Please include the bioanalytical reports and their corresponding method validation reports with the sample stability reports for the PK studies in the NDA submission as well.

In module 2.7: Clinical Summary, please include a summary of the biopharmaceutics studies and associated analytical methods and, a summary of clinical pharmacology studies.

In the NDA, describe in detail how the original formulation used in the PK study (TOP001) is linked to the proposed to-be-marketed formulation used in PK study (TOP008) and all subsequent studies including the Phase 3 clinical trials. In your description, we recommend that you apply the principles of the FDA guidance entitled: SUPAC-SS: Non-sterile Semisolid Dosage Forms; Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation located at the following website: <http://www.fda.gov/cder/guidance>.

## **Clinical**

### **Question 3:**

Is the submission of CRFs in accordance with CFR 314.50(f)(0) acceptable?

### **Response:**

Case Report Forms (CRFs) should be submitted as well as electronic links for: a) death B) all Serious AEs C) all Severe AEs D) all patients who discontinued for whatever the reason (not just because of adverse events)

CRFs that are not submitted should be readily available upon request.

Provide narrative summaries for Dropouts and Serious AEs

Provide narrative summaries for Dropouts and Serious AEs

CRFs should be referenced under the study in which it belongs and tagged as “case-report-forms” in that study’s stf.xml file.

### **Question 4:**

Does the FDA agree that a 4-month safety update is not required for this submission because Topaz will not have any ongoing studies with the 0.5% Ivermectin Cream at the time of a 4-month safety update?

### **Response:**

No, please submit a 4-month safety update. If no new safety information is available at the time of this submission then that should be stated.

### **Question 5:**

Does the FDA agree that post marketing safety surveillance of 0.5% Ivermectin Cream can be accomplished according to CFR 314.80 in combination with a patient package insert, and that a formal REMS program is not required?

### **Response:**

This will be a review issue, but at this time we are not aware of a safety signal that would necessitate a REMS.

### **Question 6:**

For a 505(b)(2) NDA filing, is following example 4 for the ISS acceptable?

### **Response:**

Yes.

### **Question 9:**

Does the FDA agree with the plans for the ISS and ISE?

for each analyte collected at Day 1 (baseline) and Day 2 by treatment group. Individual changes from Day 1 (baseline) to Day 2 will be calculated and descriptive statistics will be presented by treatment group. For the changes from Day 1 (baseline) to Day 21, possible differences between treatment groups will be assessed by ANOVA with treatment as factor.

In addition to the above analyses, please provide the following in the ISS and elsewhere in your submission as appropriate:

1. Shift tables for all laboratory values for both outside the normal range and outside the range that is considered clinically significant. Please provide the normal range of values for all parameters, the threshold for concern for a clinically significant change and your justification for why this threshold is appropriate (i.e., for CBC provide all of the above for WBC, RBC, % neutrophils, % lymph, % mono, % eos, % baso, Hcb, Hct, MCHC, RDW, PLT, MPV, etc.).
2. Group means for irritancy safety study results.
3. Frequency tables for sensitivity safety study results. Define and justify the threshold for calling a score positive (or negative) for sensitization.

For the ISE you propose to present data from studies TOP003, TOP010 (phase 2) and studies TOP011, TOP012 (phase 3). You propose to make the following comparisons:

1. Topical 0.5% Ivermectin Cream compared to vehicle control for all five studies,
2. Topical 0.5% Ivermectin Cream compared to vehicle control for TOP011 and TOP012, which are the pivotal double-blind studies,
3. Topical 0.5% Ivermectin Cream compared to vehicle control by Age Group (6 months to <2 years, 2 to <4 years, 4 to <12 years, 12 to 16 years, and >16 years old),
4. Topical 0.5% Ivermectin Cream compared to vehicle control by Gender (male or female), and
5. Topical 0.5% Ivermectin Cream compared to vehicle control by Race (White or Non-white).

TOP001 (PK), TOP007 (dermal safety) and TOP008 (PK and safety) will not be included in the ISE since their design differed substantially from the phase 3 studies.

With regard to subject disposition, frequency counts and percentages will be presented for the following by treatment group:

- Subjects who were randomized,
- Subjects included in the ITT population,
- Subjects included in the ITT2 population,
- Subjects included in the PP population,
- Subjects who discontinued early for each population, and
- Subjects who completed the study for each population.

Frequency counts and percentages of subject's reported reasons for discontinuation will be summarized.

Variables collected at the Day 1 (baseline) visit will be summarized and presented by treatment group. Descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum) will be presented for the continuous variables.

Frequency counts and percentages will be presented for the categorical variables. The following variables collected at the following visits will be presented: demographic characteristics, hair characteristics and severity of infestation.

The success rate and 95% confidence intervals for the primary efficacy endpoint will be presented for the following subgroups within each population:

- Age Group (6 months to <2 years, 2 to <4 years, 4 to <12 years, 12 to 16 years, and >16 years old)
- Gender (male or female)
- Race (White or Non-white).

For the pooled analyses described above, please provide details as to whether these analyses were performed according to a predefined protocol or were a post hoc exercise.

In addition to the above age subgroups, provide an analysis for the subgroup of adults (age 18 and older).

Provide a detailed subgroup analysis for race (i.e. beyond white vs. nonwhite).

In addition to the above pooled analysis please provide the following in the ISE and elsewhere in your submission as appropriate:

1. A detailed examination of study to study differences in results. Critical study design differences should be discussed and compared. The extent to which the results of the relevant studies reinforce or do not reinforce each other. Any major inconsistencies in the data regarding efficacy should be addressed, and any areas needing further exploration should be identified.
2. Documentation and discussion of for the amount of time spent examining subjects for the presence of lice, at baseline and the primary efficacy time point, and rationale for any time bounds specified (min or maximum times).
3. Discussion of the high vehicle response rate demonstrated in your studies, including possible explanations.
4. A rationale for why the data presented represents a demonstration of substantial evidence of effectiveness for the proposed indication.

For additional information about the content of the ISE, you are referred to the Agency Guidance: Guidance for Industry Integrated Summary of Effectiveness which is available at the FDA website

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079803.pdf>

### **Biostatistics**

There were no specific Biostatistics questions submitted. We have the following comments:

1. You stated that you used the Chi-square test to compare the ivermectin group to the vehicle group, and used the logistic regression model to assess the possible study site effects and treatment by study site interactions. It should be noted that in the SPA letter dated 12/23/2009, the Agency agreed to the sponsor's primary analysis method of using the Cochran-Mantel-Haenszel (CMH) test stratified by study sites (see Agreement #11 on the SPA letter). As such, provide analysis results of the CMH test stratified by study sites in the Study Report section of the NDA.
2. Provide the Agency with SAS transport files in electronic form. The data sets should include demographic and baseline data as well as efficacy and safety data. Data Sets should include:
  - a. The database for the Phase 3 studies should include both raw variables (from the CRF) and derived variables suitable for conducting primary and secondary efficacy analyses.
  - b. Each data set should include the treatment assignments. For each of the primary and secondary endpoints, an indicator variable that denotes whether measurements are actual or imputed should be included.
  - c. The submission should include adequate documentation for the data sets including definitions of each variable in the data set, formulas for derived variables and decodes for any factor variables so that all categories are well-defined in the documentation.
  - d. In addition to the electronic data sets, the NDA submission should include the following items:
    - o Study protocols including the statistical analysis plan, protocol amendments and their dates.
    - o The generated treatment assignment lists and the actual treatment allocations (along with date of enrollment) from the trials.

### **Additional Administrative Comments**

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND or NDA might identify additional comments or information requests.
2. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21 CFR 54 and 21CFR 314.50(k).
3. We remind you of the Pediatric Research Equity Act of 2007 which requires all applications for a new active ingredient, new dosage form, new indication, new route of administration, or

new dosing regimen to contain an assessment of the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations unless this requirement is waived or deferred.

4. You are reminded that effective June 30, 2006 all submissions must include content and format of prescribing information for human drug and biologic products based on the new Physicians Labeling Rule (see attached website <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for additional details).

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

/s/  
-----

SUSAN J WALKER  
02/18/2011



IND 073134

**MEETING MINUTES**

Topaz Pharmaceutical Inc.  
Attention: Lisa DeLuca, Ph.D.  
Vice President Regulatory Affairs  
100 Witmer Road, Suite 280  
Horsham, PA 19044

Dear Dr. DeLuca:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug and Cosmetic Act for TPZ-0434 (ivermectin) Cream, 0.5%, for the eradication of head lice in patients 6 months of age and older.

We also refer to the teleconference between representatives of your firm and the FDA on January 8, 2010. The purpose of the telecom was to discuss our December 23, 2009 Special Protocol-Agreement Letter.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant difference in understanding regarding the meeting outcomes.

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

Sincerely,

*{See appended electronic signature page}*

Jill Lindstrom, M.D.  
Clinical Team Leader  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure

## **1.0 BACKGROUND**

The sponsor requested clarification of the Agency's December 23, 2009 Special Protocol Assessment letter.

## **2. DISCUSSION**

### **Question 1:**

Topaz submitted the results from study TOP008 as per FDA request on December 3, 2009. Topaz is confused regarding the above FDA statement. Is the SPA agreement binding as of today, but might be revoked if FDA does not agree with Topaz's analysis of the TOP008 data? Please clarify.

### **Meeting Discussion:**

The Agency explained that we did not have enough data to make an agreement in regards to laboratory assessments as part of safety monitoring for the Phase 3 studies at the time the SPA agreement was made.

Further, the Agency advised that Topaz should proceed by submitting the final study report for study TOP008 for review and recommendations. However, since this study was not submitted with the SPA, there would be no agreements regarding laboratory assessments as part of safety monitoring.

### **Question 2:**

Please clarify if the FDA intends for at least 8 household per treatment arm or if the FDA intended to state 8 households per center.

### **Meeting Discussion:**

The Agency clarified that agreement number 2 in the December 3, 2009 SPA letter should read, "The number of sites planned should be defined in the protocol. The study should be planned to enroll at least 8 households per treatment arm per center."

### **Question 3:**

If revisions are made to the protocol based on comments received from the FDA does that invalidate our agreement assuming that those changes would be covered under the provisions stated on page 9 of the Guidance for Industry Special Protocol Assessment?

### **Meeting Discussion:**

The Agency clarified that a revised protocol should be officially submitted to the IND incorporating our recommendations and that the Special Protocol Assessment agreements would remain binding as long as they were not revised.

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

-----  
IND-73134

-----  
GI-1

-----  
TOPAZ  
PHARMACEUTICA  
LS LLC

-----  
TPZ-0434

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

/s/  
-----

JILL A LINDSTROM  
02/05/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 73,134

**MEETING MINUTES**

Topaz Pharmaceuticals Inc.  
Attention: Lisa DeLuca, Ph.D.  
Vice President Regulatory Affairs and Quality Assurance  
100 Witmer Road, Suite 280  
Horsham, PA 19044

Dear Dr. DeLuca:

Please refer to your Investigational New Drug Application (IND) file for TPZ-0434 (ivermectin) Cream, 0.5%, for the eradication of head lice in patients 6 months of age and older.

We also refer to the meeting between representatives of your firm and the FDA on August 12, 2009. The purpose of the meeting was to discuss the development program for TPZ-0434 (ivermectin) Cream, 0.5%.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Dawn Williams, Regulatory Project Manager at (301) 796-5376.

Sincerely,

*{See appended electronic signature page}*

Susan J. Walker, M.D., F.A.A.D.  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

---

**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** B  
**Meeting Category:** End of Phase 2

**Meeting Date and Time:** August 12, 2009 at 9:00 am  
**Meeting Location:** Food and Drug Administration, White Oak Campus

**Application Number:** IND 73,134  
**Product Name:** TPZ-0434 (ivermectin) Cream, 0.5%  
**Indication:** the eradication of head lice in patients 6 months of age and older  
**Sponsor/Applicant Name:** Topaz Pharmaceuticals Inc.

**Meeting Chair:** Susan Walker, M.D.  
**Meeting Recorder:** Dawn Williams, B.S.N.

**FDA ATTENDEES**

Susan Walker, M.D., F.A.A.D., Director, DDDP  
Jill Lindstrom, M.D., Clinical Team Leader, DDDP  
Jane Liedtka, M.D., Clinical Reviewer, DDDP  
Melinda McCord, M.D., Clinical Reviewer, DDDP  
Barbara Hill, Ph.D., Pharmacology Supervisor, DDDP  
Jerry Wang, Ph.D., Pharmacology Reviewer, DDDP  
Dawn Williams, B.S.N., Regulatory Project Manager, DDDP  
Abimbola Adebawale, Ph.D., Clinical Pharmacology Reviewer, DCPIII  
Mat Soukup, Ph.D., Biostatistics Reviewer, DB III

**SPONSOR ATTENDEES**

Thomas Beck, M.D., Chief Medical Officer  
Lisa DeLuca, Ph.D., Vice President Regulatory Affairs and Quality Assurance

(b) (6)  
William Ryan, B.V.Sc., Vice President Medical Affairs

(b) (6)  
Nicholas Spring, B.Sc. (Hons), Chief Executive Officer and Founder

## 1. BACKGROUND

Topaz Pharmaceuticals Inc. intends to file the New Drug Application (NDA) for the ivermectin cream 0.5% formulation as a 505(b)(2) application with cross reference, and without access, to the systemic safety of NDA 50-742, Stromectol tablets, approved in November of 1996.

## 2. DISCUSSION

### Regulatory

#### **Question 1:**

Does the FDA agree with Topaz' intention to file the NDA for the indication described as a 505(b)(2) application?

#### **Response:**

#### **505(b)(2) Standard background information:**

A 505(b)(2) application would be an acceptable approach at this time based on the information provided. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at <http://www.fda.gov/cder/guidance/index.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at <http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-vol1.pdf>)).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate. Identify how each section of your NDA will be supported for approval under 505(b)(2) pathway.

Be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a duplicate of that drug and eligible for approval under section 505(j) of the act, we may refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an ANDA that cites the duplicate product as the reference listed drug.

**Question 2:**

Topaz requests a partial waiver of the requirement to submit pediatric assessments with respect to the pediatric population under 6 months. Topaz requests this waiver due to the necessary studies being impossible or highly impracticable to conduct due to the small number of patients in that age group (section 505B9a(4)(B)(i) of the Act). Is the FDA willing to grant a partial waiver for infants less than 6 months?

**Response:**

A waiver for subjects under 6 months of age appears reasonable. Submit your request for a partial waiver and your certification of the grounds for a partial waiver according to 21 CFR 314.55(c)(3) in your NDA. If you intend to submit a partial waiver request based on your position that studies are impossible or highly impractical because the number of patients in that age group is small, you should include data to support your position.

**Question 3:**

Does the FDA agree that the clinical development plan for Ivermectin Cream, 0.5% will be in compliance with the Pediatric Research Equity Act?

**Question 4:**

Will the FDA accept the Ivermectin Cream, 0.5% clinical development plan as the pediatric plan?

**Response to Questions 3 and 4:**

No. The population enrolled in your pivotal trials needs to include subjects aged 6 months and older. To accomplish this, you will need to have completed your PK study in the youngest cohort prior to initiation of your pivotal trials. Enrollment of sufficient numbers of younger aged subjects will be needed to achieve an indication down to 6 months of age. Ultimately, whether you are able to include enough subjects in the younger age groups to satisfy PREA requirements will be a review issue. Submit a revised protocol for your phase 3 studies that includes this younger population for Agency review. You are referred to the draft *Guidance for Industry How to Comply with the Pediatric Research Equity Act* published in September 2005.

**Question 5:**

Based on this amendment (Act S.3560 amending Title XIX of the Social Security Act), Topaz thinks that Ivermectin is eligible for market exclusivity. Does the Agency agree?

**Response:**

This is a review issue determined at the time of approval.

**Chemistry, Manufacturing and Controls (CMC)**

**Question 6:**

The drug product is a (b) (4) containing (b) (4) water for external application to the hair. Does the FDA concur that the drug product meets the CDER Data Standards Manual dosage form definition for cream?

**Response:**

We can not make a determination on dosage form until examining a representative sample. Bring a representative sample to the End-of-Phase 2 meeting.

Be aware that the final determination of the dosage form will be made in the NDA review where you will need to submit representative samples with rheological data (shear stress versus shear rate, viscosity versus shear rate) for dosage form evaluation.

**Question 7:**

Does the FDA concur that the noncompendial excipients have been used in previously approved drug products and are not novel excipients?

**Response:**

We do not concur. We can not find (b) (4) shea butter and sorbitan tristearate in FDA's inactive ingredient data base, indicating that they have not been used in FDA approved drug products. Therefore, these three non-compendial ingredients are novel excipients. Provide the following CMC information for each novel excipient in the IND:

- Name and address of supplier
- Description for manufacturing process
- Supplier's certificate of analysis
- In-coming specification of drug product manufacturer

**Question 8:**

Is the proposal to submit the NDA containing 12 months real time stability and 6 months accelerated stability on 3 batches acceptable?

**Response:**

Yes, it is acceptable.

**Question 9:**

Is the plan to submit additional 18 months stability data during the NDA review acceptable?

**Response:**

Your NDA should be complete application at the time of submission. You can amend a NDA with more stability data but the review of a stability amendment is not guaranteed.

**Question 10:**

Topaz does not think that antimicrobial effectiveness testing (AET) is necessary for the Ivermectin Cream, 0.5% for the following reasons:

1. Product is packaged for single use

2. Microbial Limits testing is being performed throughout the stability program. Does the FDA agree that AET testing for the single use Ivermectin Cream, 0.5% is not necessary?

**Response:**

We would agree to waive USP<51>Antimicrobial Effectiveness Testing if

- (1) the stability results on Microbial Limit Test and assay on parabens are satisfactory,
- (2) at least one registration stability batch is shown to be able to meet USP<51> requirements at release and throughout the stability study period, and
- (3) you will include in the NDA a special study which shows the formulation can pass USP<51> at the lower limit of the proposed acceptance criterion of parabens.

**Question 11:**

Does the Agency agree that the stability specifications listed in Table 16 are acceptable?

**Response:**

No, we disagree. Add the following tests with appropriate acceptance criteria to the stability specification of drug product: viscosity, homogeneity, packaging integrity, and minimal fill.

**Question 12:**

The Ivermectin Cream, 0.5% will be packaged in a laminate tube

(b)

)

(4)

)

t.

- The tube materials meet the appropriate sections of the indirect food additive regulations (21 CFR 177.1520),
- The product will be applied topically, and
- The dosing regimen is for acute use.

Does the Agency agree that the issue of extractables and leachables can be addressed in the NDA by the documentation provided in the attachments for the product contact materials and the results of the stability data on the Phase 3 batches?

**Response:**

No, we disagree. Each of formulation-contacting components needs to be shown to be in compliance with USP<661>.

**Question 13:**

Given the packaging Topaz will be using, the nature of the drug, and its application, Topaz does not think that additional photostability testing of the cream and the packaged product is necessary. Does the Agency agree?

**Response:**

We disagree. Per ICHQ1B Section 3, we recommend that minimally you should test the exposed cream. If the exposed cream is shown to be photo-stable after light stress, you can end your investigation on the cream. In any event, we recommend you to follow the decision tree described in ICHQ1B.

### Additional CMC Comments

1. If you plan to rely on the Agency's findings of Stromectol (NDA 50-742) regarding systemic safety, make sure that the impurity profiles of drug substance and drug product are comparable to those of Stromectol.
2. Be advised that if the designated commercial manufacturing site for drug product is different from the Phase 3 site, appropriate bridging studies would be required. SUPAC-SS contains examples for bridging different sites.
3. In Table 12 you indicate that olive oil and oleyl alcohol function as (b) (4) in the formulation. (b) (4)

### **Meeting Discussion:**

**The sponsor provided placebo samples. They stated that they would be sending the to-be-marketed formulation samples soon.**

### Pharmacology/Toxicology

#### **Question 14:**

Does the FDA find the nonclinical package adequate to support a 505(b)(2) NDA for Ivermectin Cream, 0.5% for the single application to patients infested with *Pediculus humanus capitis* (head lice) of the scalp and hair?

#### **Response:**

If it is determined that an adequate clinical bridge has been provided between your drug product, 0.5% ivermectin cream, and Stromectol® tablets, then the nonclinical studies you have conducted appear to be adequate to support a 505(b)(2) NDA submission for your drug product.

In the absence of an adequate clinical bridge, a NDA for the product should be supported by complete nonclinical information (including repeat dose toxicology data, reproductive and developmental toxicology data, and genetic toxicology data). Note that you cannot directly cite data to which you do not have a right to refer, even if the Agency reviews or other documents may allude to such data, and we cannot directly utilize our knowledge of such data on your behalf.

A 505(b)(2) application may rely upon nonclinical information derived from published literature for which the sponsor does not have the right to the underlying data. However, the adequacy of published data to support any aspect of the development of the product will be a review issue. Published reports considered to be pivotal to the review process (i.e., that are key to addressing a

safety issue) need to provide detailed data and methodology that are suitable for in-depth review. If we find that adequately detailed information is not contained in a published report that is submitted to address a pivotal safety issue, then you may be asked to submit additional information (i.e., either obtain and submit a detailed report of the study that was published or else conduct a new study).

One possibility for providing complete nonclinical information in the absence of a clinical bridge would be to obtain a right of reference letter for the approved drug product which would allow the Agency to use the safety data available for the approved drug product to support the development of your drug product. The adequacy of the safety data available through a right of reference letter for an approved drug product to support any aspect of the development of your drug product will be a review issue.

In the absence of either a clinical bridge, right of reference letter or adequate published literature reports, you would need to conduct the appropriate nonclinical toxicology studies per the ICH M3 document, "Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals" that outlines the scope and timeline of the recommended nonclinical development program for a drug product.

### **Clinical Pharmacology/Biopharmaceutics/Clinical**

#### **Question 15:**

Does the FDA agree that an adequate systemic bridge to Stromectol has been established, and that the FDA can rely on the findings of systemic safety for Stromectol tablets to support a 505(b)(2) NDA application for Ivermectin Cream, 0.5%?

#### **Response:**

We cannot agree that an adequate systemic bridge to Stromectol has been established since you are proposing to conduct some additional PK studies which may impact the adequacy of the bridge. We have the following comments:

You propose to construct a bridge to use the Agency findings of systemic safety for Stromectol tablets (NDA 050742) which are approved for patients weighing 15 kg and above. You intend to use these findings to support your need for nonclinical studies.

The clinical component of your development plan that is relevant to the systemic safety bridge consist of the findings from the Phase 1 study (TOP – 001) which compared 0.5% ivermectin cream topically to oral ivermectin and to a topical placebo in children ages 4-10 with head lice infestation. In addition, the results of your proposed PK study with a target enrollment of 5 children aged 6 months through 3 years will be needed to inform the systemic safety bridge. Note that the targeted enrollment of 5 subjects for this PK study may not be adequate to evaluate the systemic exposure in this age group. We recommend that you enroll a minimum of 15 subjects (similar to what you have for the 4- 10 year olds) with a minimum of 12 evaluable subjects completing the study with at least half of the subjects below the age of 2.

Ultimately, the adequacy of the bridge is a review issue; however, the framework for the bridge appears adequate. In study TPO – 001, which used an assay with a sensitivity of 5 ng/ml, you stated that no systemic absorption of ivermectin was detected following the topical application of 0.5 % ivermectin cream. We acknowledge your proposal to utilize a more sensitive assay (compared to the one used in study TOP-001) for the planned PK study in ages 6 month to 3 years to estimate the relative exposure more precisely in this age group. The results of this study will also impact the adequacy of the bridge.

The sponsor is encouraged to submit the protocol for the planned PK study in subjects aged 6 months to 3 years old for Agency review with sufficient lead time to allow for adequate review and comments to be sent back to the sponsor. We remind you that you will need to have completed your PK study in the youngest cohort prior to initiation of your pivotal trials (see Regulatory section, Response to Questions 3 and 4).

**Meeting Discussion:**

**The sponsor stated that they anticipate having a new assay with a sensitivity of about 50 pg/ml.**

**The Agency stated that the data from the PK study in the youngest cohort could inform the need for laboratory monitoring in the phase 3 trials.**

**Clinical/Biostatistics**

**Question 16:**

Does the FDA find the overall clinical development package adequate to support a 505(b)(2) NDA filing for Ivermectin Cream, 0.5% for the following indication: (b) (4)

**Response:**

The population proposed for your Phase 3 trials, subjects over 15 kg, will not support an indication for (b) (4)

(b) (4). The population treated in your pivotal studies needs to include subjects aged 6 months and older and would therefore include subjects in the < 15 kg weight range. Submit a revised protocol for your phase 3 studies that includes this younger (and lighter) population for Agency review.

The study design you propose which involves two phases, one placebo-controlled and the other an open-label roll-over study is not acceptable. You propose to re-treat with the Ivermectin Cream in an open-label fashion a subgroup of consenting subjects who have failed treatment based on the observation of live lice at day 2. It is not appropriate to treat an infested subject with an investigational agent without proven efficacy when they have failed to respond to the agent initially. The failed subjects should be offered rescue treatment with an approved product.

In your protocol for the phase 3 trials you fail to provide information about the duration of the treatment application. In addition, you do not provide the instructions that will be given to the subject at the time the Ivermectin 0.5% cream is dispensed. Provide a written list of the detailed instructions to be given to the subject regarding application of the Ivermectin Cream at home. This should include the duration of therapy and any ancillary recommendations.

Ultimately, the indication for your product will rest on the designs, conduct and outcomes of the studies relied on to support approval. The word “<sup>(b) (4)</sup>” may not be included in the final wording for the indication.

The framework that you provide; dermal safety studies, 2 multicenter, randomized, placebo-controlled trials, one PK study in ages 6 months to 3 years, appears acceptable to support the filing of an NDA for your product.

You propose to conduct the appropriate topical safety studies, a cumulative irritation study in 30 subjects and a contact sensitization study in 200 subjects. This is acceptable.

**Question 17:**

Will the endpoints selected for the Phase 3 trials support the intended indication?

**Response:**

The proposed primary efficacy endpoint, the proportion within each treatment group of index subjects who are lice free on day 14 (14 days post last treatment), appears appropriate once the age of the studied population is revised as suggested above in the response to Question #16. The secondary efficacy endpoint of the proportion within each treatment group of all subjects who are lice free on day 14 (again with the revised population), also appears appropriate.

As previously noted in the response to Question #16, the Agency does not recommend including an open-label roll-over treatment phase (as proposed in the current protocol) with Ivermectin. Removing this phase B from the protocol would result in the second secondary efficacy endpoint proposal (the proportion of subjects who are lice free on day 15 in the open label extension) no longer being relevant.

**Question 18:**

Does the FDA agree that the proposed safety evaluations for the Phase 3 trials are adequate? These evaluations include the following: scalp/skin and ocular assessments (refer to Attachment 1, Phase 3 Protocol, Section 10.8.2)?

**Response:**

In the briefing document you propose to provide additional information on safety via an open-label study in 15 children < 15 kg during which laboratory assessments (for CBC's and LFT's) will be performed. In your revised protocol which includes subjects 6 months and older in the pivotal trials, it would be appropriate to assess these same laboratory values in a subset of the younger subjects, thereby obviating the need for a separate trial.

You should specify at what timepoint after application the subjects will be assessed for ocular irritation. The timepoint that you select should be that which you would anticipate as being most likely to manifest ocular irritation.

The scales provided for measurements of erythema and pruritus appear adequate. The scales for measurement of excoriation and pyoderma are not clearly defined and some categories overlap. You should improve your assessment scales for measurement of excoriation and pyoderma.

**Question 19:**

The statistical plans for the Phase 3 studies are described in the Phase 3 Protocol (refer to Attachment 1, Phase 3 Protocol, Section 14). Does the FDA concur with the included analyses?

**Response:**

Two Phase 3 trials in subjects with head lice infestations would be sufficient to support the efficacy of your product.

As statistical superiority alone may not be sufficient for establishing the efficacy of ivermectin cream, you should propose a clinically meaningful difference as well as null and alternative hypotheses. The trial should also be powered to detect this difference.

**Meeting Discussion:**

**The sponsor proposed a treatment of effect of 30% as the clinically meaningful difference. The Division requested details to be provided in a Phase 3 protocol.**

**Question 20:**

Is the total planned exposure of children less than 15 kg sufficient to allow the use of the drug in this patient population per the final label?

**Response:**

As previously noted in the response to question #18; your need to revise your protocol to include subjects 6 months and older in your pivotal trials. It would also be appropriate to assess the laboratory values suggested for your open-label trial in children under 15 kg in a subset of the younger subjects in your pivotal trials, thereby obviating the need for a separate trial.

The final content of the label will be determined by the design and outcome of your phase 3 studies including the details of the population treated. If you fail to recruit a sufficient number of younger subjects this will be reflected in labeling.

**Question 21:**

Given that Topaz plans to file the NDA as a 505(b)(2), will the FDA confirm that the total number of subjects exposed to Ivermectin Cream, 0.5% to be included in the safety data base in support of this NDA will be adequate?

**Response:**

new dosing regimen to contain an assessment of the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations unless this requirement is waived or deferred.

5. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry: Qualifying for Pediatric Exclusivity for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.
6. In response to a final rule published February 11, 1998, the regulations 21 CFR 314.50(d)(5)(v) and 314.50(d)(5)(vi)(a) were amended to require sponsors to present safety and effectiveness data "by gender, age, and racial subgroups" in an NDA. Therefore, as you are gathering your data and compiling your NDA, we request that you include this demographic analysis.
7. In your clinical development program, you will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). Please plan to address this issue early in development.
8. We remind you that effective June 30, 2006, all submissions must include content and format of prescribing information for human drug and biologic products based on the new Physicians Labeling Rule (see attached website <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for additional details).
9. You are encouraged to request a Pre-NDA Meeting at the appropriate time.
10. If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for a listed drug, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug. {Add a statement here *specific to the proposed product* regarding the need for data and information that establishes that reliance is scientifically justified (i.e., "bridging" data)} If you intend to rely on literature or other studies that you have no right of reference to but that are necessary for approval, you also must establish that reliance on the studies is scientifically appropriate.

Your question suggests that you are proposing to reference information from the Summary Basis of Approval (SBA) or FDA reviewers' public summaries for support of safety and/or efficacy. We note that a 505(b)(2) applicant that seeks to rely upon the Agency's finding of safety and/or effectiveness for a listed drug, may rely only on that finding as is reflected in the approved labeling for the listed drug.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
IND 73134	GI 1	TOPAZ PHARMACEUTICA LS LLC	TPZ-0434
IND 73134	GI 1	TOPAZ PHARMACEUTICA LS LLC	TPZ-0434

---

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

---

/s/

---

SUSAN J WALKER  
08/26/2009



IND 73,134

(b) (4)

Attention:

(b) (6)

(b) (6)

(b) (6)

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for TPZ-0434 Ivermectin 0.5% Treatment Conditioner.

We also refer to the teleconference between representatives of your firm and the FDA on November 14, 2008. The purpose of the meeting was to discuss your clinical development plan and the FDA's letter dated October 16, 2008 for TPZ-0434 Ivermectin 0.5% Treatment Conditioner.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Paule Elie, Regulatory Project Manager at (301) 796-2110.

Sincerely,

*{See appended electronic signature page}*

Susan J. Walker, M.D., F.A.A.D.  
Director  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

**MEMORANDUM OF TELECONFERENCE**

**DATE:** November 14, 2008

**APPLICATION:** IND 73,134 - TPZ-0434 Ivermectin 0.5% Treatment Conditioner

**FDA Participants:**

Division of Dermatology and Dental Products

Susan J. Walker, M.D., Director

Jill Lindstrom, M.D., Clinical Team Leader

Jane Liedtka, M.D., Clinical Reviewer

Maria Walsh, RN, MS, Acting Associate Director for Regulatory Affairs

Paule Elie, MPH, Regulatory Project Manager

Division of Biostatistics III

Mohamed Alish, Ph.D, Team Lead Biometrics

Mat Soukup, Ph.D, Biometrics Reviewer

**Sponsor Participants:**

Topaz Pharmaceuticals Inc/ (b) (4)

Lisa DeLuca, Ph.D, Vice President of Regulatory Affairs

Nicholas Spring, BSc President and CEO

William Ryan, BVSc, MRCVS, VP of Clinical and Medical Affairs

Michael Corrado, MD Chief Scientific Officer

(b) (6)

**SUBJECT:** Phase 2 Dose-Ranging Trial

**BACKGROUND INFORMATION:**

The sponsor submitted a Type A meeting request on October 21, 2008 to discuss FDA's recommendation to conduct an appropriately designed Phase 2 dose-ranging trial prior to conducting a Phase 3 trial as communicated in FDA's letter dated October 16, 2008.

The sponsor posed the following question in the meeting request:

Ivermectin has an established safety profile from systemic use in humans, and its insecticidal effectiveness has been confirmed in controlled animal studies and clinical reports of use in humans. In development of a novel ivermectin product to treat head lice, Topaz Pharmaceuticals had two key objectives: first, to develop a formulation with a concentration low enough to avoid transdermal absorption through the scalp; and second, a concentration high enough to allow a quick and reliable kill of lice thereby achieving a clinical cure while reducing the risk that head lice resistance to the product will emerge. The company thinks that the current data and proposed

studies address the central issues of dose justification for a product intended for the safe and effective acute treatment of head lice infestation in adults and children.

*Does the Division agree that the sponsor has identified an appropriate dose to take into Phase 3 trials?*

**SUMMARY OF TELECONFERENCE:**

- The sponsor presented a summary of information to support the position that a Phase 2 dose-ranging trial is not necessary.
- The Agency said it does not agree that the information submitted by the sponsor is sufficient to eliminate the need for a Phase 2 dose-ranging trial.
- The Agency reiterated its recommendation that an appropriately designed Phase 2 dose-ranging trial be conducted from which efficacy results can be used to power Phase 3 trials per the October 16, 2008 letter. However, the Agency said the sponsor may proceed with their Phase 3 trial “at their own risk”.
- The Agency asked whether the sponsor had initiated studies; they stated that they had not based upon the Agency’s previous recommendations.
- The Agency strongly recommended that the sponsor request an End-of-Phase 2 (EOP2) meeting, to discuss the Phase 2 data and the Phase 3 trial design.
- The Agency stated that the Phase 3 design methodologies were deficient, and recommended that the sponsor include a revised Phase 3 protocol in the EOP2 meeting package.
- The Agency recommended that the sponsor submit a Special Protocol Assessment (SPA) to the Agency following the EOP2 meeting, and referred the sponsor to the guidance document regarding an SPA submission.
- The Agency emphasized that a Phase 3 protocol submitted routinely would not necessarily receive a review in 45 days unless it were submitted as an SPA per the guidance.
- The Sponsor stated that they understood all of the above recommendations that the Agency clarified. The call was then concluded.

Linked Applications

Sponsor Name

Drug Name / Subject

-----  
IND 73134

-----  
TOPAZ  
PHARMACEUTICALS  
LLC

-----  
TPZ-0434

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

/s/  
-----

SUSAN J WALKER  
12/22/2008



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

PIND 73,134

(b) (4)  
(b) (6)

(b) (6)

Please refer to your Pre-Investigational New Drug Application (PIND) file for TPZ-0434 (ivermectin) Shampoo/Condition.

We also refer to the teleconference between representatives of your firm and the FDA on July 24, 2006. The purpose of the meeting was to obtain the Agency's input on the suitability of your planned clinical studies.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Margo Owens, Regulatory Project Manager, at (301) 796-2110.

Sincerely,

*{See appended electronic signature page}*

Susan Walker, M.D.  
Director  
Division of Dermatology and Dental  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES



**Meeting Date:** July 24, 2006                      **Time:** 2:00  
**Location:** WO 4266                                      **Meeting ID:** 8700  
**Topic:** TPZ-0434 (Ivermectin) Shampoo/Conditioner for the treatment of head lice  
**Subject:** Pre-IND meeting  
**Regulatory Path:** 505(b)(2) proposed  
**Listed Drug:** Stromectol tablets  
  
**Sponsor:** Topaz Pharmaceutical, LLC.  
  
**Meeting Chair:** Susan Walker, M.D./Division Director, DDDP  
  
**Meeting Recorder:** Margo Owens/Regulatory Project Manager, DDDP

**FDA Attendees:**

Susan Walker, M.D./Director, DDDP  
Paul Brown, Ph.D./Supervisor, Pharmacology, DDDDP, HFD-540  
Barbara Hill, Ph.D./Pharmacology Reviewer, DDDDP, HFD-540  
Shulin Ding, Ph.D./ Pharmaceutical Assessment Lead, ONDQA  
Dennis Bashaw, Pharm.D./Team Leader, Pharmacokinetics, DPEIII, HFD-880  
Tapash Ghosh, Ph.D./Pharmacokinetics Reviewer, DPEIII, HFD-880  
Markham Luke, M.D., Ph.D./Team Leader, Clinical, DDDP, HFD-540  
David Kettl, M.D./Clinical Reviewer. DDDDP, HFD-540  
Mohamed Al-Osh, Ph.D./Team Leader, Biostatistics, DBIII, HFD-725  
Donald Hare, Ph.D./Special Assistant to the Director, OGD, HFD-604  
Margo Owens/Regulatory Project Manager, DDDDP, HFD-540  
Wayne Mitchell /ORP/DRPII

**Sponsor Attendees:**

**Topaz Pharmaceuticals LLC.**  
Nick Spring, President and Co-Founder

(b) (4)  
(b) (6)

**Purpose:**

The sponsor requests input from the Agency on the suitability of the planned Clinical studies. The pre-meeting briefing document (submitted June 23, 2006) provides background and questions (p 4) for discussion.

### **Chemistry, Manufacturing and Controls:**

CMC questions were not submitted by the sponsor for this meeting. After reviewing the limited CMC information provided in the briefing package, we have the following comments for the sponsor:

1. Are you planning to make a reference to a DMF for the drug substance?
2. Please provide in the IND a UV/Vis spectrum (220-700 nm) for both drug substance and drug product at a concentration relevant to clinical studies.
3. Please clarify the formulation which you plan to develop. We note that a formulation composition table is provided in the meeting request dated Feb. 22, 2006 but not in the meeting briefing package.
4. Please include a consideration of dose standardization in the design of container/closure system for the proposed drug product.

You are advised to refer to CDER Guidance for Industry “Content and format for investigational new drug applications (INDs) for Phase 1 studies of drugs, including well-characterized, therapeutic, biotechnology-derived products” for the recommended information to support an IND submission.

### **Pharmacology/Toxicology:**

There were no Pharmacology/Toxicology questions identified in this briefing document. The Agency has the following comments.

### **Agency:**

If an adequate clinical bridge can be formed between the ivermectin shampoo/conditioner drug product and Stromectol tablets, then the Agency could rely on our findings of systemic safety for the Stromectol tablets NDA application to support a 505(b)(2) NDA application for the ivermectin shampoo/conditioner drug product. In the absence of a clinical bridge, then the sponsor would need to provide complete nonclinical toxicology information (i.e., repeat dose toxicology data, reproductive and developmental toxicology data and genetic toxicology data) either from studies conducted by the sponsor or possibly from references from the scientific literature (that are deemed adequate). The Agency does not consider use of the nonclinical toxicology information contained in the “Ivermectin (WHO Food Additives Series 27)” reference referred to in the Investigator’s brochure as adequate to support the safety of the ivermectin shampoo/conditioner drug product. The nonclinical toxicology information contained in the “Ivermectin (WHO Food Additives Series 27)” reference is summary information and does not provide data from full study reports. In addition, it is not clear that it would be appropriate to use this information to support the safety of the ivermectin shampoo/conditioner drug product since much of the information summarized in this reference appears to be the property of the Stromectol tablet NDA sponsor. Another option for providing complete nonclinical toxicology information for ivermectin to support the safety of the ivermectin shampoo/conditioner drug product would be to obtain a right of reference letter from the Stromectol tablet NDA sponsor.

An adequate nonclinical toxicology package would need to be included with the original IND submission to support initiation of clinical studies. The sponsor is referred to the ICH M3 guidance document titled "Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals" (<http://www.fda.gov/cder/guidance/1855fnl.pdf>), which outlines the scope and timeline of the recommended nonclinical development program for a new drug product.

It is not clear what will be the final formulation for the drug product and if it may contain unqualified excipients based on the information provided in the briefing package. The sponsor is referred to the Guidance for Industry document titled "Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients" ([www.fda.gov/cder/guidance/5544fnl.htm](http://www.fda.gov/cder/guidance/5544fnl.htm)), which outlines the scope and timeline of the recommended nonclinical development program for unqualified excipients.

The following additional nonclinical toxicology studies are recommended for the ivermectin shampoo/conditioner drug product prior to initiation of clinical studies even if the sponsor is able to obtain rights to use the nonclinical safety data contained in the Stromectol tablet NDA via forming a clinical bridge or obtaining a right of reference letter.

- 1) A nonclinical dermal irritation study.
- 2) A nonclinical ocular irritation study.
- 3) A nonclinical sensitization study.
- 4) A two-week repeat dose dermal toxicology study in a non-rodent species (preferably minipigs). It is recommended that this study incorporate use of an untreated control group, vehicle control group and 3 dose groups that vary the concentration of the active in the clinical vehicle formulation. It is recommended that the high dose group in repeat dose nonrodent dermal toxicology studies be the maximum feasible dose (i.e., maximum feasible concentration and maximum feasible volume applied over at least 10% of total body surface area), if tolerated. It is recommended that complete hematology, clinical chemistry, histopathology and toxicokinetics be evaluated in repeat dose nonrodent dermal toxicology studies. In addition, it is recommended that EKG evaluation be incorporated into this study.

Note: It should be emphasized that because complete data are not currently available, the perceived nonclinical data requirements may change during review of an IND. All pivotal toxicology studies should be conducted in compliance with Good Laboratory Practice regulations (21 CFR58). The sponsor is invited to submit draft protocols for pivotal toxicology studies to the Division for comment prior to initiation of those studies. In the IND, please clearly identify the exact formulation of all test materials used in all nonclinical studies. The sponsor is encouraged to submit in the IND photocopies of any published literature that it believes is relevant to the IND. An effort should be made to present a balanced representation of the database (both "pro" and "con" articles should be cited and discussed, if they are available). All statements in the IND that concern safety should be supported by actual data, not just summaries of data.

### **Clinical Pharmacology/Biopharmaceutics:**

There were no Clinical Pharmacology/Biopharmaceutics questions identified in this briefing document. The Agency has the following comments.

#### **Agency:**

- Under a 505(b)(2) rubric, in order to support a clinical bridge to the pre-clinical data (see Pharm/Tox comments above), the sponsor should consider including a systemic treatment arm (using the approved stomectol tablet) in the PK protocol.
- Generally a complete PK profile needs to include sampling for 5 half-lives for an adequate PK characterization. Ivermectin has a  $t_{1/2}$  of about 18 hours, thus the proposed, 24 hours of PK sampling may not be enough. However, given that the product is a shampoo with a limited contact time, prior to rinsing, the sponsor should incorporate PK sampling into the follow-up study visits where hair samples will be collected for ivermectin content analysis. The sponsor should make sure that analysis of ivermectin for a pivotal PK study would be done with a validated and sensitive assay method.
- The pivotal PK study should be conducted in the target patient population with the final market formulation. In case the formulation changes over time, the sponsor may have to conduct an additional PK study depending upon the nature of changes in the formulations to maintain the bridge to the pre-clinical data.
- The sponsor needs to document the amount of shampoo that will be applied to each patient in the protocol. In case the amount varies from subject to subject based on the hair length and other factors, the amount applied needs to be recorded so that the amount (dose) applied can be standardized for future calculation purposes.
- Whether the sponsor plans to use same amount or different amount of the proposed product to the patients, they should include analysis to demonstrate mass balance between amount applied and total amount accounted from systemic uptake, hair rinse and hair content. In addition, the patients should be stratified to have adequate representation of each age group, gender and hair length.

### **Clinical:**

#### **Sponsor's Clinical Question 1:**

Topaz plans to conduct a phase 1 PK/tolerance study in 12 healthy subjects, 9 active and 3 placebo. Based on the results from the phase 1 study, one phase 3 study versus placebo will be conducted. Assuming the results from the phase 3 study are positive, would this development plan support a claim for efficacy in the proposed indication of head lice?

#### **Agency's Response:**

No phase 2 dose-ranging plans are included in the briefing document. The sponsor is encouraged to conduct phase 2 studies to investigate safety and efficacy at various ranges of concentration, duration of application, and frequency of treatment. Please clarify your rationale for a four minute application time. See also Biostatistics comments below.

*The sponsor clarified their reluctance to perform phase 2 trials by stating that they already have compelling evidence that 0.5% shampoo paralyzed adult lice within 15 seconds.*

*Phase 2 studies were encouraged by the Agency in order to determine sample size information so they would avoid the risk for under-powering phase 3 trials.*

*The sponsor indicated that they would consider using a wide tooth comb, not for lice or nit removal, but as a method to distribute the residual drug product along the entire length of the hair.*

The sponsor should also consider standardization of dosage and the potential for dosing variability in both the PK and later clinical studies. The amount of shampoo/conditioner applied should be known and measured. Individual differences in hair length characteristics should be considered.

Typically, two well controlled clinical studies are recommended for phase 3 to establish efficacy and safety.

*The sponsor stated that they would provide more information regarding the phase 3 trials. The Agency reinforced the recommendation that two adequately designed and powered trials would ensure replication of clinical results. Please see additional statistical comments below.*

Head lice is an issue primarily, but not exclusively, for pediatric patients. Safety in pediatric patients would need to be explored prior to phase 3 trials. Study populations should mirror the anticipated population to be treated.

In addition to dose ranging and safety information, topical safety studies are required prior to marketing, and typically include dermal irritation, dermal sensitization, phototoxicity and photoallergenicity. The cumulative irritancy studies should include at least 35 evaluable subjects, and the contact allergy studies at least 200 evaluable subjects. Phototoxicity and photoallergenicity studies may be waived if there are no ingredients in the product that absorb in the 290 – 700 nM spectrum. Phototoxicity studies, if required, should include at least 30 evaluable subjects, and photoallergenicity studies should be conducted in at least 45 evaluable subjects. Topical safety studies should be performed on the final to-be-marketed formulation.

**Sponsor’s Clinical Question 2:**

Topaz proposes to evaluate approximately 325 subjects (approximately 244 active and 81 placebo) for the phase 3 clinical trial. Based upon all of the historical information on ivermectin in humans, Topaz feels that this would be an adequate safety population for this indication. Does the Agency consider that 325 subjects would be sufficient to support the safety?

**Agency’s Response:**

It is premature to determine if this number of subjects will be adequate until the safety profile of the topical drug is better described.

The current labeling for Stromectol® (ivermectin tablets) states that safety and effectiveness in pediatric patients weighing less than 15 kg have not been established. Clinical experience in this patient population is limited. The sponsor should propose a strategy for any proposed labeling

for the topical product that would address this concern. There is also at least one report of excess mortality in an elderly population treated with ivermectin for scabies.

In designing endpoints for the clinical trials, any development plan should take into account the life cycle of the head louse and the ability of viable nits to hatch into adult forms after treatment. The sponsor's proposed assessment may not be sufficient.

**Sponsor's Clinical Question 3:**

Since this formulation of 0.5% ivermectin shampoo/conditioner will be applied as a topical and is not expected to be readily absorbed systemically, Topaz does not plan to conduct a QTc study to test for cardiac repolarization. Does the Agency concur that this type of study is not required?

**Agency's Response:**

A decision regarding the need for a "thorough" QT/QTc study will be affected by the results of the PK absorption studies and animal studies. EKG's are recommended for the initial PK study. The sponsor is referred to the ICH E14 guidance for further information.

**Biostatistics:**

**Sponsor's Question 1:**

Topaz plans to conduct a Phase 1 PK/tolerance study in 12 healthy subjects, 9 active and 3 placebo. Based upon the results from the Phase 1 study, one Phase 3 study versus placebo will be conducted. Assuming the results from the Phase 3 study are positive, would this development plan support a claim for efficacy in the proposed indication of head lice?

**Agency's Response:**

- It is difficult to provide detailed statistical comments based on the protocol synopses. The sponsor proposed a sample size of 325 subjects and treatment application duration of 4 minutes for their Phase 3 trial without providing any rationale. As drug development is a sequential process, the Division recommends the sponsor to conduct a dose ranging Phase 2 study to investigate dose concentration, treatment application duration and frequency of use, before planning Phase 3 trials. The results from an adequately designed Phase 2 trial should be used to plan future Phase 3 trials. The treatment effect estimate of the selected dose from the Phase 2 trial should be used to power the Phase 3 trials.
- To establish efficacy, the Division usually requires replication of the study findings and thus 2 Phase 3 studies.

Following the completion of the Phase 2 trial, the sponsor is encouraged to request a meeting with the Agency and submit a full protocol of their planned Phase 3 trials for Agency comments and concurrence.

*The sponsor indicated that the proposed number of patients in the current submission of 325 subjects was based on assumed response rate of 90% for the active and 20% for the vehicle. Further, they noted that they would rather proceed from Phase 1 to Phase 3 trials without conducting Phase 2 dose-ranging study as they already have information about drug concentration and treatment duration, and they would use lower estimate of success rate than 90% when powering Phase 3 trials. In response, the Division stated as powering future Phase 3 trials is still based on assumptions concerning response rates the sponsor is taking risk of under powering Phase 3 trials, and the Division still recommends conducting Phase 2 trial to learn about safety and efficacy before proceeding to Phase 3 trials.*

*The sponsor inquired whether one large study vis-à-vis two ‘relevant’ statistical studies would be acceptable for filling future NDA. In response the Division stated that for replication of study findings efficacy should be established, through formal statistical testing, based on results of 2 Phase 3 trials. The sponsor stated that for some NDA submissions for this indication results from one Phase 3 trial was used to support an efficacy claim. The Division stated that this might be the case for a 3-arm trial which involves already approved products; and that the sponsor should provide specific cases of one Phase 3 study submission which they are referring to.*

**505(b)(2) Strategy:**

*The sponsor stated the following:*

*1) A bridging study will be conducted in Phase 1 to compare the systemic absorption of ivermectin from the shampoo with the oral formulation. If the study demonstrates that there is no systemic absorption, or is below that of the oral formulation then the sponsor would refer to the Agency's finding of safety for the oral formulation for the traditional toxicology studies.*

*2) The pivotal trials will be our proposed product versus placebo (i.e., the same shampoo formulation without ivermectin).*

*The Agency clarified that if absorption greater than zero is demonstrated, we will have to look at the data to inform our decision. More studies may be needed since the risk/benefit calculation for the oral ivermectin indication is not the same as for the treatment of lice.*

**Project Management:**

**Agency:**

1. For applications submitted after February 2, 1999, per 21CFR 54.3 and 21CFR 54.4, an NDA applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests.
2. Comments shared today with the sponsor are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today’s discussion. Review of the information submitted to the IND might identify additional comments or information requests.
3. Based on the repeal of section 507 of the Food, Drug and Cosmetic Act, the Sponsor is advised that ivermectin would not be eligible for marketing exclusivity. The Sponsor may refer to the guidance document issued by the Agency in May 1998, *Guidance for Industry and Reviewers Repeal of Section 507 of the Federal Food, Drug, and Cosmetic Act*. This guidance document defines the administrative actions required by the agency for reviewing and approving antibiotic drug applications that were submitted after November 21, 1997. The Sponsor may also refer to the *Federal Register* notice 99N-3088, *Marketing Exclusivity and Patent Provisions for Certain Antibiotic Drugs* issued January 24, 2000, which lists the active drug substances, including any derivative thereof, that are directly affected by the repeal of Section 507.

4. The sponsor is encouraged to request an End of Phase 2 Meeting at the appropriate time.
5. The sponsor is reminded of the Pediatric Research Equity Act of 2003 which requires all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred.
6. Your pre-IND has been assigned #73,134. Please reference this number on all submissions and correspondence. **Please note, studies in humans may not be conducted under this PIND.** Before you may conduct studies in humans, you must submit an Investigational New Drug Application (IND, see 21 CFR Part 312).

Minutes Preparer: \_\_\_\_\_  
Margo Owens/Regulatory Project Manager DDDP

Chair Concurrence: \_\_\_\_\_  
Susan Walker, M.D./Director, DDDP

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

/s/

-----  
Susan Walker

8/23/2006 06:20:33 PM