

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209570Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 209570	NDA Supplement # Not Applicable	If NDA, Efficacy Supplement Type: Not Applicable <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: None Established/Proper Name: Benznidazole Dosage Form: Tablet 100 mg and 12.5 mg		Applicant: Chemo Research, S.L. Agent for Applicant (if applicable): Exeltis USA, Inc.
RPM: Gregory DiBernardo		Division: Anti-Infective Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p style="margin: 0;"><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p style="margin-left: 20px;"> <input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: August 29, 2017 </p> <p style="margin-left: 20px;"><i>Note: 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.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>August 29, 2017</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain: Applicant did not seek Subpart H Approval path, but Division determined this was the path for Approval for NDA, so no promotional materials were submitted with NDA.		<input type="checkbox"/> Received Division determined Subpart H was path for approval promotional materials requested in 8/29/17 Action letter.
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(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).

³ 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.

Review priority: Standard Priority
 Chemical classification (new NDAs only): Type 1 New Molecular Entity (NME)
(confirm chemical classification at time of approval)

- | | |
|---|---|
| <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 checked="" type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
- Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
- Submitted in response to a PMC
- Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
- Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 <i>(approvals only)</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications <i>(approvals only)</i>	
<ul style="list-style-type: none"> • Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> • Indicate what types (if any) of information were issued 	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
<ul style="list-style-type: none"> • Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes n/a
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> • Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list <i>(approvals only)</i>	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action and date: Approval, August 29, 2017
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> • Most-recent draft labeling 	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	March 17, 2017; July 7, 2017 (WD), August 11, 2017
<ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) 	
<ul style="list-style-type: none"> • Review(s) (<i>indicate date(s)</i>) 	March 15, 2017; August 10, 2017
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: March 9, 2017 DMEPA: May 25, July 26, and August 24, 2017 DPMH: July 5, 2017 OPDP: July 24, 2017 Product Quality August 20, 2017 PLT: July 26, 2017 CSS: <input checked="" type="checkbox"/> None DMPP/PLT (DRISK): <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	March 9, 2017
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	August 14, 2017
❖ NDAs/NDA supplements only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>Has Orphan Product Designation</u> 	
❖ Breakthrough Therapy Designation	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>)	2/23 (2), 3/9, 3/17, 4/13, 5/10, 7/7, and 7/26/17
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	6/21/17 Meeting Minutes DMEPA-PNR; 8/7/17 Meeting Minutes DMEPA-PNR
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> • Pre-NDA meeting (<i>indicate date of mtg</i>) 	September 30, 2016
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	April 12, 2017
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	June 27, 2017
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	No other meetings
❖ Advisory Committee Meeting	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> • Date(s) of Meeting(s) 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	August 29, 2017
Division Director Summary Review (<i>indicate date for each review</i>)	August 29, 2017
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	August 29, 2017
PMR/PMC Development Templates (<i>indicate total number</i>)	3

Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Clinical review(s) <i>(indicate date for each review)</i>	August 4, 2017
• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not <i>(indicate date of review/memo)</i>	August 4, 2017/Clinical Review page 78
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i> ⁵	CDRH June 9, 2017
❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> • REMS Documents and REMS Supporting Document <i>(indicate date(s) of submission(s))</i> • REMS Memo(s) and letter(s) <i>(indicate date(s))</i> • Risk management review(s) and recommendations (including those by OSE and CSS) <i>(indicate date of each review and indicate location/date if incorporated into another review)</i> 	n/a n/a May 24, 2017
❖ OSI Clinical Inspection Review Summary(ies) <i>(include copies of OSI letters to investigators)</i>	August 3, 2017
Clinical Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	June 12, 2017
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) <i>(indicate date for each review)</i>	June 7, 2017, June 20, 2017
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	June 7, 2017
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	May 17, 2017 & August 22, 2017

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).

Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	July 19, 2017
❖ 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
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)	August 20, 2017
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<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>)	June 5, 2017 & August 20, 2017
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	n/a
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	n/a
❖ Facilities Review/Inspection	
<input type="checkbox"/> Facilities inspections (<i>indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection (e.g., new strength, manufacturing process, or manufacturing site change)</i>)	<input checked="" type="checkbox"/> Acceptable 6/7/17 <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(Notify CDER OND IO)</i>
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input checked="" type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done <i>(Send email to CDER OND IO)</i>
❖ For products that need to be added to the flush list (generally opioids): Flush List <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done
❖ Take Action Package (if in paper) down to Document Room for scanning within two business days	<input checked="" type="checkbox"/> Done

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/s/

GREGORY F DIBERNARDO
08/31/2017



NDA 209570

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Chemo Research, S.L.
c/o Exeltis USA, Inc.
180 Park Avenue, Suite 101
Florham Park, NJ 07928

ATTENTION: Sandy S. Suh, PharmD
Head, Regulatory Affairs (R&D)

Dear Dr. Suh:

Please refer to your New Drug Application (NDA) dated and received December 29, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Benznidazole Tablets, 12.5 mg and 100 mg.

We also refer to your correspondence dated and received July 19, 2017, requesting review of your proposed proprietary name, (b) (4)

We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

We object to the proposed proprietary name (b) (4) because, as proposed, it would overstate the efficacy of the drug and minimize the risks associated with the drug. The proposed proprietary name contains the word (b) (4) which is defined as (b) (4) (http://unabridged.merriam-webster.com/unabridged (b) (4), accessed 7/25/17). According to your draft product labeling this drug is indicated, “in pediatric patients (2 to 12 years of age) for the treatment of American Trypanosomiasis (Chagas disease) caused by Trypanosoma cruzi. This indication is approved under accelerated approval based on (b) (4) the number of treated patients who became IgG antibody negative against the recombinant antigens of T. cruzi. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. . . .” The proposed proprietary name may misleadingly suggest (b) (4) (w) (4) However, the draft product labeling does not include any information to support this benefit or conclusion. We are not aware of clinical trials being designed and conducted to support such a conclusion. Furthermore, (b) (4) (b) (4)

(b) (4) Therefore, the proposed proprietary name (u) (4) would be misleading.

Please note that the Federal Food, Drug, and Cosmetic Act (FD&C Act) provides that labeling or advertising can misbrand a product if misleading representations are made (See 21 U.S.C. 321(n)). The FD&C Act also provides that a drug is misbranded if its labeling is false or misleading in any particular (21 U.S.C. 352(a)). A proprietary name, which appears in labeling, could result in such misbranding if it is false or misleading, such as by making misrepresentations with respect to safety or efficacy.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review.

If you require additional information on developing proprietary names for drugs, proposing alternative proprietary names for consideration, or requesting reconsideration of our decision, we refer you to the following:

- Draft Guidance for Industry Best Practices in Developing Proprietary Names for Drugs, (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf>)
- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet G. Higgins, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-0330. For any other information regarding this application, contact Gregory DiBernardo, Regulatory Project Manager in the Office of New Drugs, at (301) 796-4063.

Sincerely,

{See appended electronic signature page}

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

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/s/

TODD D BRIDGES
08/11/2017

TELECONFERENCE MEETING MINUTES

Meeting Date Friday, August 4, 2017
Time: 12:10 PM – 12:30 AM EST
Meeting Location: White Oak Building 22, Room 4311

Application Number: NDA 209570

Product Name and Strength: (b) (4) (benznidazole) tablet
12.5 mg tablet and 100 mg tablet
Applicant/Sponsor Name: Chemo Research, S. L.

Call-In Information: 888-585-9008
Meeting ID: (b) (4)

Meeting Chair: Otto L. Townsend, Pharm D , Acting Team Leader

FDA Participants: Division of Medication Error Prevention and Analysis (DMEPA)
Sevan Kolejian, Pharm D, Safety Evaluator
Otto L. Townsend, Pharm D , Acting Team Leader
Irene Z. Chan, PharmD, BCPS, Deputy Director

Office of Surveillance and Epidemiology (OSE)
Janet Higgins, Senior Regulatory Project Manager

Division of Anti-Infective Products (DAIP)
Maureen P. Dillon Parker, Chief, Regulatory Project Manager

Sponsor Participants: Marta Burgaz, PhD, Project Manager and CMC Manager
Sandy Suh, PharmD, Regulatory Affairs

MEETING OBJECTIVES

The purpose of this teleconference is to notify Applicant of our preliminary findings for the proposed proprietary name, (b) (4)

BACKGROUND

Chemo Research submitted a Request for Proprietary Name Review on July 19, 2017, to review the proposed proprietary name, (b) (4).

For reference (previous names found unacceptable)

- (b) (4)
- (b) (4)

DMEPA CONCERNS WITH THE PROPOSED PROPRIETARY NAME

We requested this teleconference to notify you of our decision regarding your proposed proprietary name, (b) (4) submitted under NDA 209570.

As proposed, the proprietary name (b) (4) would overstate the efficacy of the drug and minimize the risks associated with the drug.

The proposed proprietary name contains the word (b) (4)

Merriam-Webster dictionary defines (b) (4) as (b) (4)
(b) (4)

According to the current version of the draft product labeling this drug is indicated, “in pediatric patients (2 to 12 years of age) for the treatment of American Trypanosomiasis (Chagas disease) caused by *Trypanosoma cruzi*. This indication is approved under accelerated approval based on (b) (4) the number of treated patients who became IgG antibody negative against the recombinant antigens of *T. cruzi*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. . . .”

The proposed proprietary name may misleadingly suggest (b) (4)
(b) (4)

However, the draft product labeling does not include any information to support this benefit conclusion. We are not aware of clinical trials being designed and conducted to support such a conclusion.

Furthermore, (b) (4)
(b) (4)

For the reasons stated, the proposed proprietary name (b) (4) would be misleading.

Federal Food, Drug, and Cosmetic Act

According to the Federal Food, Drug, and Cosmetic Act (FD&C Act) labeling or advertising can misbrand a product if misleading representations are made (See 21 U.S.C. 321(n)).

A drug is misbranded if its labeling is false or misleading in any particular (21 U.S.C. 352(a)). A

proprietary name, which appears in labeling, could result in such misbranding if it is false or misleading, such as by making misrepresentations with respect to safety or efficacy.

Thus, we are issuing a denial letter for this name that you will be receiving in the near future.

REGULATORY OPTIONS FOR THE PROPOSED PROPRIETARY NAME

Denial of the proposed name, (b) (4) will be sent soon. If desired, submit another proposed name for our consideration.

DISCUSSION

DMEPA expressed their concerns with the proposed proprietary name and the Applicant was notified that the Agency will be sending a denial letter for the reasons stated above. The Agency acknowledged that their PDUFA goal date is quickly approaching that that 90 days for a proprietary name review does not exist prior to the target action date. DMEPA stated that they would work with the Applicant if the Applicant submits a new proposed name quickly.

NEXT STEPS/ACTION ITEMS:

The Agency will await the Applicant's response of the desired actions regarding this proprietary name.

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/s/

JANET G HIGGINS
08/07/2017

From: [DiBernardo, Gregory](#)
To: "Sandy Suh"
Subject: FDA Communication: NDA 209570-benznidazole-CHEMO-DMEPA Carton/Container IR/Comments
Date: Wednesday, July 26, 2017 4:48:54 PM
Importance: High

Hello Dr. Suh,

I would like to provide the Division of Medication Error and Analysis comments on your July 19, 2017, submission of carton and container labels:

The product strength statement should be more prominent than the product quantity statement on the container labels and carton labeling (see 21 CFR 201.15(a)(6)). Increase the strength statement's prominence on the container label and carton labeling. Also, increasing the prominence of the strength statement, can help address the risk of confusion between the 12.5 mg and 100 mg strengths. We have received postmarket medication errors reports describing product selection errors when a product's quantity (100) has been misinterpreted as the product's strength (100 mg) and vice versa. This medication error type has occurred when products are available in a quantity of 100 and available in multiple strengths including 100 mg.

Please be aware that there will be **no paper/hardcopy** communication to follow this email communication. Please submit your response to this information request officially to your NDA.

Thank you,

Gregory F. DiBernardo

Regulatory Project Manager
FDA/CDER/OND/OAP/Division of Anti-Infective Products
10903 New Hampshire Avenue
Building 22, Room 6223
Silver Spring, MD 20993
Telephone: (301) 796-4063

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/s/

GREGORY F DIBERNARDO
07/26/2017



NDA 209570

**PROPRIETARY NAME REQUEST
WITHDRAWN**

Chemo Research, S.L.
c/o Exeltis USA, Inc.
180 Park Avenue, Suite 101
Florham Park, NJ 07928

ATTENTION: Sandy S. Suh, PharmD
Head, Regulatory Affairs

Dear Dr. Suh:

Please refer to your New Drug Application (NDA) dated and received December 29, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Benznidazole Tablets, 12.5 mg and 100 mg.

We also refer to:

- Your correspondence, dated and received April 7, 2017, requesting review of your proposed proprietary name, (b) (4)
- Your correspondence, dated and received June 29, 2017, notifying us you are withdrawing your request for a review of the proposed proprietary name, (b) (4).

This proprietary name request is considered withdrawn as of June 29, 2017.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, a new request for a proposed proprietary name review should be submitted. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet G. Higgins, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-0330. For any other information regarding this application, contact Gregory DiBernardo, Regulatory Project Manager in the Office of New Drugs, at (301) 796-4063.

Sincerely,

{See appended electronic signature page}

Janet G. Higgins
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

JANET G HIGGINS
07/07/2017

TELECONFERENCE MEETING MINUTES

Meeting Date Friday, June 16, 2017
Time: 09:10 AM – 09:25 AM EST
Meeting Location: White Oak Building 22, Room 6320

Application Number: NDA 209570

Product Name and Strength: (b) (4) (benznidazole) tablet
12.5 mg tablet and 100 mg tablet
Applicant/Sponsor Name: Chemo Research, S. L.

Call-In Information: 888-585-9008
Meeting ID: (b) (6)

Meeting Chair: Irene Z. Chan, PharmD, BCPS, Deputy Director

FDA Participants: Division of Medication Error Prevention and Analysis (DMEPA)
Sevan Kolejian, Pharm D, Safety Evaluator
Otto L. Townsend, Pharm D , Acting Team Leader
Irene Z. Chan, PharmD, BCPS, Deputy Director

Office of Surveillance and Epidemiology (OSE)
Janet Higgins, Senior Regulatory Project Manager

Division of Anti-Infective Products (DAIP)
Maureen P. Dillon Parker, Chief, Regulatory Project Manager
Abimbola O. Adebowale, PhD, Associate Director of Labeling

Sponsor Participants: Enrico Colli, MD, Chief Scientific Officer
Marta Burgaz, PhD, Project Manager and CMC Manager
Sandy Suh, PharmD, Regulatory Affairs

MEETING OBJECTIVES

The purpose of this teleconference is to notify Applicant of our preliminary findings for the proposed proprietary name, (b) (4)

BACKGROUND

Chemo Research submitted a Request for Proprietary Name Review on April 7, 2017, to review the proposed proprietary name, (b) (4)

Previously, the Applicant submitted the proposed proprietary name, (b) (4) on January 5, 2017. However, the Division of Medication Error Prevention and Analysis (DMEPA) found the name, (b) (4)

unacceptable due to orthographic similarity and overlapping product characteristics with the proprietary name, (b) (4). The PDUFA date for this NDA is August 29, 2017.

DMEPA CONCERNS WITH THE PROPOSED PROPRIETARY NAME

We requested this teleconference to notify you of our preliminary safety concerns with your proposed proprietary name, (b) (4) submitted under NDA 209570.

The proposed proprietary name, (b) (4), is similar in spelling and pronunciation to the currently marketed product, (b) (4)

This similarity in spelling between the names stems from a direct overlap of four letters in similar positions (b) (4). Additionally, both names have three syllables, the second and third syllables of the name pair are nearly indistinguishable when pronounced (b) (4)

Additionally, we note that the names have orthographic similarity. The orthographic similarity between the names stems from the fact that both names contain seven letters with four identical letters (b) (4) appearing in the same position in both names. We acknowledge the names begin with different letters (b) (4) however, given the orthographic similarity of the rest of the name, this difference may not be sufficient to mitigate the risk of confusion.

The orthographic and phonetic similarity of this name pair is further supported by the FDA's Phonetic and Orthographic Computer Analysis (POCA), which calculates a combined score of 74% for this name pair and a phonetic only score of 85%, indicating that this name pair is highly similar.

In addition to the orthographic similarities, both products share overlapping product characteristics, which increase the potential for wrong drug errors. (b) (4) have numerical similarity in strength (*100 mg vs. 1,0000 units/10ml (1000 units/ml)*) and dose (*100 mg vs. 1000 units*). We acknowledge that the two products have different frequency of administration (b) (4) *12 hours vs. three times weekly*, different routes of administration (*oral vs. intramuscular*) as well as different dosage forms (*tablet vs. injection*). However, frequency of administration may be overlooked or omitted or the product may be ordered with a frequency of 'one time' in some healthcare settings. Also, since both products are available in a single dosage form (*tablet versus injection*), and are given by a single route of administration (*oral vs. intramuscular*), dosage form and route of administration may not be included on prescriptions to distinguish these two products. Postmarketing evidence indicates name confusion has occurred between products that have different frequency of administration and where there are different dosage forms or routes of administration. For example, there are documented cases of confusion between Latuda (*oral tablet*) and Lantus (*subcutaneous*

injection)¹, and Cerebyx (*injectable solution*) and Celebrex (*oral capsule*)², which show that name confusion may lead to errors despite differing product characteristics.

We acknowledge that our conclusion differs from the external study submitted in support of the proposed proprietary name, (b) (4). However, the trademark vulnerability evaluation conducted by Med-ERRS, that was performed using the ERRS MODEL[®] of analysis, did not perform a safety assessment of this name pair.

REGULATORY OPTIONS FOR THE PROPOSED PROPRIETARY NAME

1. Request that we finalize our name review for (b) (4) by the proprietary name PDUFA date of July 6, 2017.
2. Withdraw the proposed name (b) (4) and submit another proposed name for our consideration.

DISCUSSION

DMEPA expressed their concerns with the proposed proprietary name and regulatory options as outline above. The Applicant inquired if action could be taken on their NDA without a proprietary name. The Agency stated that lack of an acceptable proprietary name would not delay action.

The Applicant stated that they would like to have some internal discussion regarding the two options discussed and would respond via email with their intent early next week. If they should decide to withdraw their name they were instructed to submit their intent officially to the application along with their courtesy response via email to Janet Higgins.

NEXT STEPS/ACTION ITEMS

The Agency will await the Applicant's response of their desired actions regarding this proprietary name.

¹ Institute for Safe Medication Practices. Safety briefs: Include purpose on Rx. ISMP Med Saf Alert Acute Care. 2011;16(17):1-2.3

² Institute for Safe Medication Practices. Errors and near misses prompt warning to practitioners and a call to rename CELEBREX. ISMP Med Saf Alert Acute Care. 1999; (7):1.

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/s/

RUTH L MADURO
06/21/2017



NDA 209570

MID-CYCLE COMMUNICATION

Chemo Research, S.L.
c/o Exeltis USA, Inc.
Attention: Sandy S. Suh, Pharm.D.
Head, Regulatory Affairs (R&D)
180 Park Avenue, Suite 101
Florham Park, NJ 07928

Dear Dr. Suh:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (benznidazole) tablet 100 mg and 12.5 mg.

We also refer to the teleconference between representatives of your firm and the FDA on April 12, 2017. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, M.D., M.P.H.
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: April 12, 2017 at 2:00 PM

Application Number: NDA 209570

Product Name: Benznidazole

Indication: Treatment of Chagas disease

Applicant Name: Chemo Research, S.L.

Meeting Chair: Thomas Smith, M.D.

Meeting Recorder: Gregory DiBernardo

FDA ATTENDEES

Office of Antimicrobial Products (OAP)

John J. Farley, M.D., M.P.H. Deputy Director

Division of Anti-Infective Products (DAIP)

Sumathi Nambiar, M.D., M.P.H.	Director
Joseph G. Toerner, M.D., M.P.H.	Deputy Director for Safety
Thomas D. Smith, M.D.	Cross Discipline Team Leader
Maria Allende, M.D.	Clinical Reviewer
Shukal Bala, Ph.D.	Clinical Microbiology Reviewer
Terry Miller, Ph.D.	Pharmacology/Toxicology Team Leader
James Wild, Ph.D.	Pharmacology/Toxicology Reviewer
Abimbola O. Adebowale, Ph.D.	Associate Director of Labeling
Maureen P. Dillon-Parker	Chief, Project Management Staff
Gregory F. DiBernardo	Regulatory Project Manager

Division of Clinical Pharmacology IV (DCP IV)

Kellie Reynolds, Ph.D.	Deputy Director
Jeffry Florian, Ph.D.	Clinical Pharmacology Team Leader
Abhay Joshi, Ph.D.	Clinical Pharmacology Reviewer

Division of Biometrics IV (DBIV)

Daphne TY Lin, Ph.D.	Deputy Division Director
Janelle Charles, Ph.D.	Biostatistics Reviewer
Felicia Griffin, Ph.D.	Biostatistics Reviewer

Office of Pharmaceutical Quality (OPQ)

Dorota M. Matecka, Ph.D. Chemistry, Manufacturing, and Controls (CMC) Lead
Katherine Windsor, Ph.D. Product Quality Reviewer

Office of Surveillance and Epidemiology (OSE)

Janet Higgins Regulatory Project Manager
Sevan Kolejian, Pharm.D. DMEPA Reviewer
Naomi Redd, Pharm.D. DRISK Team Leader
Natasha Pratt, Ph.D. DEPI Reviewer

Office of Scientific Investigation (OSI)

Janice Pohlman, M.D., M.P.H. Team Leader

Center for Device and Radiologic Health (CDRH)

David Goodwin, Ph.D. Lead Reviewer
Noel Gerald, Ph.D. Biology Reviewer

APPLICANT ATTENDEES

CHEMO Research

Enrico Colli, M.D. Chief Scientific Officer
Marta Gómez Burgaz, Ph.D. CMC Manager and Project Manager

Exeltis USA, Inc.

Sandy S. Suh, Pharm.D. Head, Regulatory Affairs (R&D)

(b) (4)

1.0 INTRODUCTION

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

2.0 SIGNIFICANT ISSUES

Clinical:

We are evaluating the relationship between the AT and F29 ELISA responses in the de Andrade and Sosa Estani studies and seroreversion with conventional serologies. The studies must establish that these responses are reasonably likely to predict clinical benefit.

The interpretation of the primary endpoint of a negative PCR used in the DNDi and Molina trials, is still unclear regarding clinical benefit in the adult population. In addition, the product used in these studies is the LAFEPE benznidazole and we have not received an adequate bioequivalence comparison between this product and yours.

3.0 INFORMATION REQUESTS

Responses pending for the information requests dated:

March 28, 2017; Chemistry, Manufacturing, and Controls (CMC)
We note that a partial response was submitted on April 10, 2017.

April 3, 2017; Nonclinical

April 4, 2017 (2); Clinical

April 7, 2017; Clinical Microbiology and Biostatistics

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

There are no major safety concerns identified at this time and there is currently no need for a REMS.

5.0 ADVISORY COMMITTEE MEETING

There are no plans at this time for an advisory committee meeting.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

The late cycle meeting date is June 27, 2017, at 3:00 PM at FDA White Oak campus.

7.0 MEETING DISCUSSION POINTS

- Chemo Research acknowledged that there continues to be an issue to acquire the requested pharmacokinetic (PK) data to bridge their benznidazole product to the LAFEPE benznidazole product. Chemo Research also noted it would be unlikely that they could acquire these data.
- FDA plans to provide labeling comments by May 28, 2017.

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/s/

SUMATHI NAMBIAR
05/10/2017



NDA 209570

**PROPRIETARY NAME
ACKNOWLEDGEMENT**

Chemo Research, S.L.
c/o Exeltis USA, Inc.
180 Park Avenue, Suite 101
Florham Park, NJ 07928

ATTENTION: Sandy S. Suh, PharmD
Head, Regulatory Affairs

Dear Dr. Suh:

Please refer to your New Drug Application (NDA) dated and received December 29, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Benznidazole Tablets, 12.5mg and 100 mg.

We acknowledge receipt of your correspondence dated and received on April 7, 2017, requesting a review of your proposed proprietary name, (b) (4)

If the application is filed, the user fee goal date will be July 6, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet G. Higgins, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-0330. For any other information regarding this application, contact Gregory DiBernardo, Regulatory Project Manager, in the Office of New Drugs at (301) 796- 4063.

Sincerely,

{See appended electronic signature page}

Janet G. Higgins
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

JANET G HIGGINS
04/13/2017



NDA 209570

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Chemo Research, S.L.
c/o Exeltis USA, Inc.
180 Park Avenue, Suite 101
Florham Park, NJ 07928

ATTENTION: Sandy S. Suh, PharmD
Head, Regulatory Affairs

Dear Dr. Suh:

Please refer to your New Drug Application (NDA) dated and received December 29, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Benznidazole Tablets, 12.5 mg and 100 mg.

We also refer to your correspondence dated and received January 5, 2017, requesting review of your proposed proprietary name, (b) (4)

We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

The proposed proprietary name, (b) (4) is orthographically similar to the approved product, (b) (4)

The orthographic similarity between the names stems from the fact that the name pair is similar in length (six letters vs. seven letters), shares the same first two letters (b) (4) and same fourth letter (b) (4). Both names also have a similar shape prefix (b) (4) and infix (b) (4) which may appear similar when scripted. We acknowledge that (b) (4) contains an additional upstroke letter (7th position, letter (b) (4)) that is not present in (b) (4) however, given the orthographic similarity of the rest of the name, this difference may not be sufficient to mitigate the risk of confusion. The orthographic similarity is further supported by the FDA's Phonetic and Orthographic Computer Analysis (POCA), which calculates a combined score of 63% for this name pair (orthographic score of 73%).

In addition to the orthographic similarities, both products share overlapping product characteristics, which increase the potential for wrong drug errors (b) (4) have overlapping strength (100 mg) and weight-based dose (b) (4)

(b) (4) Since both products are dosed based on patient weight, the strength or mg/kg dose may not be included on a prescription; however, the calculated weight based dose may be the same, for example, for pediatric patient weighing 40 kg, (b) (4) (b) (4) thus, there is the potential for dose-dose overlap between the two products.

We acknowledge that the two products have different frequency of administration (b) (4) (b) (4) different routes of administration (*oral vs. intravenous*) as well as different dosage forms (*tablet vs. injection*). However, frequency of administration may be overlooked or omitted as product may be ordered with a frequency of ‘once’ in various healthcare settings. Also, since both products are available in a single dosage form (*tablet versus injection*), and are given by a single route of administration (*oral vs. intravenous*), dosage form and route of administration may not be included on prescriptions to distinguish these two products. Postmarketing evidence indicates name confusion has occurred between products that have different frequency of administration and where there are different dosage forms and/or routes of administration. Documented cases of confusion between Pradaxa (*twice daily*)¹ and Plavix (*once daily*)¹, Advicor (*oral tablet*) and Advair (*inhaled powder*)², and Cerebyx (*injectable solution*) and Celebrex (*oral capsule*)³ show that name confusion may lead to errors despite the differences in frequency of administration, route of administration and dosage form.

We acknowledge that our conclusion differs from the external study submitted in support of the proposed proprietary name (b) (4). The trademark vulnerability evaluation conducted by Med-ERRS, that was performed using the ERRS MODEL[®] of analysis, did not perform a safety assessment of this name pair.

Therefore, based on orthographic similarities and overlapping product characteristics we find the proposed name, (b) (4) is vulnerable to confusion with the currently marketed product, (b) (4)

We note that you have proposed an alternate proprietary name in your submission dated January 5, 2017. In order to initiate the review of the alternate proprietary name, (b) (4) submit a new complete request for proprietary name review. The review of this alternate name will not be initiated until the new submission is received.

If you require additional information on developing proprietary names for drugs, proposing alternative proprietary names for consideration, or requesting reconsideration of our decision, we refer you to the following:

- Draft Guidance for Industry Best Practices in Developing Proprietary Names for Drugs, (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf>)

¹ Institute for Safe Medication Practices. Safety Briefs: Arixtra is not a hemostat. ISMP Med Saf Alert Acute Care. 2012;17(21):1-4.

² Institute for Safe Medication Practices. Safety briefs: Advair-Advicor mix-up. ISMP Med Saf Alert Community/Ambulatory Care. 2003; 2(8): 1-2.

³ Institute for Safe Medication Practices. Errors and near misses prompt warning to practitioners and a call to rename CELEBREX. ISMP Med Saf Alert Acute Care. 1999; (7):1.

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet G. Higgins, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-0330. For any other information regarding this application, contact Gregory DiBernardo, Regulatory Project Manager, in the Office of New Drugs at (301) 796-4063.

Sincerely,

{See appended electronic signature page}

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

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/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
03/17/2017



NDA 209570

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Chemo Research, S.L.
c/o Exeltis USA Inc.
Attention: Sandy S. Suh, Pharm.D.
Head, Regulatory Affairs (R&D)
180 Park Avenue, Suite 101
Florham Park, NJ 07928

Dear Dr. Suh:

Please refer to your New Drug Application (NDA) dated December 29, 2016, received December 29, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for (b) (4) (benznidazole) Tablets 100 mg and 12.5 mg.

We also refer to your amendments dated February 24, 2017 (2).

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 **Priority**. Therefore, the user fee goal date is August 29, 2017. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V:

<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

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, mid-cycle, 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 requirement/commitment requests by May 28, 2017. This date conforms to the 21st Century Review timeline for your application. If our review continues on an expedited timeline, we may communicate revised dates for labeling and postmarketing requirement/commitment requests.

In addition, the planned date for our internal mid-cycle review meeting is March 29, 2017. We are not currently planning to hold an advisory committee meeting to discuss this application.

If your 505(b)(2) application relies on FDA's finding of safety and/or effectiveness for a listed drug and contains a paragraph IV certification, this filing communication is the "paragraph IV acknowledgment letter" described in 21 CFR 314.52(b) and the "postmark" is 4 calendar days after the date on which this letter is signed. Notice of the paragraph IV certification must be sent to the persons described in 21 CFR 314.52(a) no later than 20 days after the date of the postmark on this paragraph IV acknowledgment letter and must contain the information described in 21 CFR 314.52(c).

At this time, we are notifying you that, we have not identified any potential review issues. Note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed,

professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

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.

Because the drug or this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, M.D., M.P.H.
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

SUMATHI NAMBIAR
03/09/2017



NDA 209570

PRIORITY REVIEW DESIGNATION

Chemo Research, S.L.
c/o Exeltis USA Inc.
Attention: Sandy S. Suh, Pharm.D.
Head, Regulatory Affairs (R&D)
180 Park Avenue, Suite 101
Florham Park, NJ 07928

Dear Dr. Suh:

Please refer to your New Drug Application (NDA) dated December 29, 2016, received December 29, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for (b) (4) (benznidazole) Tablet 100 mg and 12.5 mg.

We also refer to your submissions dated January 5, January 25, February 17, and February 22, 2017.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is August 29, 2017.

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, mid-cycle, 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 requirement/commitment requests by May 28, 2017.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before March 13, 2017.

If you have any questions, call Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

Sincerely,

{See appended electronic signature page}

Maureen P. Dillon-Parker
Chief, Project Management Staff
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

MAUREEN P DILLON PARKER
02/23/2017



NDA 209570

NDA ACKNOWLEDGMENT

Chemo Research, S.L.
c/o Exeltis USA Inc.
Attention: Sandy S. Suh, Pharm.D.
Head, Regulatory Affairs (R&D)
180 Park Avenue, Suite 101
Florham Park, NJ 07928

Dear Dr. Suh:

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: (b) (4) (benznidazole) Tablet 100 mg and 12.5 mg

Date of Application: December 29, 2016

Date of Receipt: December 29, 2016

Our Reference Number: NDA 209570

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 February 27, 2017, 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 Anti-Infective Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is **required** for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

Sincerely,

{See appended electronic signature page}

Maureen P. Dillon-Parker
Chief, Project Management Staff
Division of Anti-Infective Products
Office of Antimicrobial Products
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/

MAUREEN P DILLON PARKER
02/23/2017



PIND 118976

MEETING MINUTES

CHEMO Research

c/o [REDACTED] (b) (4)

Attention: [REDACTED] (b) (4)

[REDACTED] (b) (4)

Dear [REDACTED] (b) (4)

Please refer to your Pre-Investigational New Drug Application (PIND) file for benznidazole.

We also refer to the meeting between representatives of your firm and the FDA on September 30, 2016. The purpose of the meeting was to discuss the planned 505(b)(2) New Drug Application (NDA) for the treatment of Chagas disease.

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

If you have any questions, call Mr. Gregory DiBernardo, Regulatory Project Manager, (301) 796-4063.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, M.D., M.P.H.
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: B

Meeting Category: Pre-NDA

Meeting Date and Time: September 30, 2016, at 11:00 AM to 12:00 PM

Meeting Location: White Oak Campus, Building 22

Application Number: PIND 118976

Product Name: Benznidazole

Indication: Treatment of Chagas Disease

Sponsor Name: CHEMO Research

Meeting Chair: Sumathi Nambiar, M.D., M.P.H.

Meeting Recorder: Gregory DiBernardo

FDA ATTENDEES - Agency

Office of Antimicrobial Products (OAP)

John J. Farley, M.D., M.P.H. Deputy Director

Division of Anti-Infective Products (DAIP)

Sumathi Nambiar, M.D., M.P.H.	Director
Dmitri Iarikov, M.D., Ph.D.	Acting Deputy Director
Joseph Toerner, M.D., M.P.H.	Deputy Director for Safety
Thomas Smith, M.D.	Clinical Team Leader
Maria Allende, M.D.	Clinical Reviewer
Lynette Berkeley, Ph.D.	Acting Clinical Microbiology Team Leader
Shukal Bala, Ph.D.	Clinical Microbiology Reviewer
James Wild, Ph.D.	Pharmacology/Toxicology Reviewer
MAJ William McCalmont, Ph.D.	Pharmacology/Toxicology Fellow
Maureen Dillon-Parker	Chief, Project Management Staff
Gregory F. DiBernardo	Regulatory Project Manager
Silvia Scalan, Ph.D.	CFP Fellow

Division of Clinical Pharmacology IV (DCP IV)

Philip Colangelo, Pharm.D., Ph.D.	Clinical Pharmacology Team Leader
Zhixia (Grace) Yan, Ph.D.	Clinical Pharmacology Reviewer

Division of Biometrics IV (DBIV)

Karen Higgins, Sc.D.	Biostatistics Team Leader
Cheryl Dixon, Ph.D.	Biostatistics Reviewer

Office of Pharmaceutical Quality (OPQ)

Dorota M. Matecka, Ph.D.	Chemistry, Manufacturing, and Controls (CMC) Lead
Yong Wang, Ph.D.	CMC Reviewer

Center for Devices and Radiologic Health (CDRH)

David Goodwin, Ph.D.	Biologist
Noel Gerald, Ph.D.	Biologist

SPONSOR ATTENDEES

CHEMO Research

Marta Gomez Burgaz, Ph.D.	CMC Manager and Project Manager, LPRI Division
Enrico Colli, M.D.	Chief Scientific Officer, LPRI Division
Belen Liebana, Pharm.D.	Clinical Operations Manager, LPRI Division

Consultants

Sandy Suh, Pharm.D	Regulatory Affairs, Exeltis USA
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(b) (4)

1.0 BACKGROUND

A PIND meeting request was submitted by CHEMO Research (CHEMO) to the FDA (Agency) on July 15, 2016, to discuss the planned 505(b)(2) NDA for the treatment of Chagas disease. The Division of Anti-Infective Products (Division) granted a September 30, 2016, meeting on August 4, 2016. CHEMO submitted a meeting package on August 30, 2016. On September 26, 2016, FDA issued Preliminary Responses to the questions contained in the meeting package (appended). CHEMO informed FDA via email communication on September 29, 2016, that they would like further discussion on all questions except 9.3(c) and 9.3(d).

2.0 DISCUSSION

9.1 Chemistry, Manufacturing, and Controls

Does the FDA agree with the content, structure, and electronic Common Technical Document (eCTD) format for presenting Chemistry Manufacturing and Controls (CMC) information provided for Module 2.3 and Module 3?

FDA Response:

The content and structure for Module 2.3 and Module 3 in eCTD format appear to be acceptable. For more information for submissions in electronic format, refer to FDA Guidance for Industry; Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions using the eCTD Specifications. Also, please refer to the FDA Additional Comments, below.

We note that drug product registration batches are manufactured with the drug substance from (b) (4), and drug product batches used in development were manufactured with the drug substance from (b) (4). We remind you of the Agency recommendations regarding the bridging of the two API sources and other CMC recommendations for your drug substance and the drug product provided in the correspondences dated May 11, and May 27, 2016.

Discussion:

CHEMO stated that they are aware of the bridging recommendations of the two API sources and the other CMC recommendations provided by the Agency and noted that this information will be included in the NDA submission. CHEMO stated they will include data for 3 batches from each API manufacturer and they will also comply with other Agency recommendations.

9.2 Nonclinical

Does the FDA agree with the content, structure, and eCTD format for presenting nonclinical information provided for Modules 2.4/2.6 and Module 4?

FDA Response:

Pharmacology/Toxicology:

The general content, structure, and eCTD format for the nonclinical safety pharmacology, pharmacokinetic, and toxicology information to be provided in Modules 2.4/2.6 and Module 4 as summarized Tables 9 and 10 of the Meeting Package are acceptable, except some of the studies previously included in the March 24, 2016, submission are not included. Please include the studies listed below. In Module 4, all of the non-literature reports listed in Table 9 should be included in full study reports and all of the literature reports listed in Table 10 should be included in their entirety including English translations when necessary.

1. DNDi. (2009). Study report no. CDCO_DNDI_09_032_PK: Pharmacokinetics of EPL-BS0063 in male Sprague Dawley rats following IV and oral administration.
2. DNDi. (2009). Study report no. CDCO_DNDI_09_029_DDI: Assessment of potential CYP3A4 inhibition by twenty four compounds using a substrate specific interaction approach in human liver microsomes.

Clinical Microbiology:

It appears from Table 9 that one microbiology study “A potential for development of resistance and activity against different lineages of *T. cruzi*” will be included in Module 4.2.3.7.7 and five studies will be included in Module 4.2.1.1. However, some of the studies which were listed in submission dated March 24, 2016, to support *in vitro* and *in vivo* activity of benznidazole against *T. cruzi* were not listed in this submission. It will aid in our review if all microbiology studies, published or unpublished that include details of the experimental design and results, are included in Module 4. English translation of any of the studies that are published in a foreign language should be included. All microbiology studies should be summarized under the subheadings that include mechanism of action, activity *in vitro* and in animal models, as well as drug resistance in Module 2.

Discussion:

CHEMO stated that all the studies included in the March 24, 2016, submission will be submitted in the NDA and that they were inadvertently omitted from the meeting package.

9.3 Clinical

a) Six clinical studies were conducted between 1991 and 2015 by various investigators. Chemo Research has been able to gain access to study related source information, including certain patient-level data. Does the Division consider the data that Chemo Research is proposing to submit sufficient for the Division’s review of a 505(b)(2) NDA for BNZ for the treatment of Chagas disease?

FDA Response:

The source data from the six studies listed seem to be adequate for the review of an NDA. Data that correlate clinical outcomes to assay results will be critical. If, in the studies conducted in the adult population, such as the Molina study of benznidazole vs. posaconazole and the Morillo study (BENEFIT), some serology data were collected as a secondary endpoint, it will be helpful for the review. In the NDA please provide a justification to link serological responses and clinical outcomes.

It is highly desirable that you provide as much source information as possible from studies that correlate clinical outcomes with PCR assays or serological responses in children and/or adults. For example, source data from the Fabbro 2007, Streiger 2004, and the Viotti 2006 studies could be helpful to support a bridge between treatment, serological responses and clinical outcomes. These studies provide data on untreated patients, and will help to understand outcomes in untreated disease. As discussed previously, data on natural history of untreated disease in neonates and children ages 0 to 6 years old will be essential (b) (4) in that age group. The therapeutic effect needs to be demonstrated with a comparison of outcomes of treated patients to the outcomes of those with untreated disease. If you believe that efficacy in children under 6 years of age can be extrapolated from a finding of efficacy in older children, you will need to show that the course of the disease (persistent serological positivity, clinical phases of the disease) and the effects of the drug are sufficiently similar in both groups.

Discussion:

CHEMO stated they will include source data from 6 key studies, including serological data if available, even if it was only a secondary endpoint.

CHEMO stated that there was no serology data from the Morillo (BENEFIT) study, and limited serology data from the Molina study. CHEMO clarified that the “four controlled studies” they will provide source data from are: DNDi E1224, Molina, Sosa-Estani and De Andrade. From the Sosa-Estani and De Andrade studies only ADaM-like data will be available. All data will be provided in English.

CHEMO stated that a sample of datasets as requested by the Agency will be provided from these studies to check the quality of the datasets. These data will be sent in a separate communication.

CHEMO stated they will provide a thorough analysis of all studies and will include additional data to correlate clinical outcomes with serological responses in children and/or adults in the NDA. Regarding data on outcomes for treated vs. untreated disease in the 0 to 6-year-old cohort; CHEMO will prepare a scientific rationale to extrapolate efficacy outcomes to this subgroup from older children. CHEMO also mentioned that Cerisola (1969) study included a cohort of 18 untreated patients to describe the natural evolution of the disease, as well as that of 133 treated children. This series has 16 children less than 6 years old who were followed for 18 months.

CHEMO stated they will take the Agency’s recommendation on collecting source data from key studies and will make all efforts to submit all these data. CHEMO stated they have made requests to all key investigators for these source data, but unfortunately they cannot guarantee these investigators can provide this information. CHEMO emphasized they are committed to do their best to get any available source data.

CHEMO stated they will synthesize all available information as part of the complete NDA submission, but in reality they may not have all source data at the time of NDA submission. Additional source data obtained may need to be submitted after the NDA is submitted in mid to late November 2016 (See **3.0 OTHER IMPORTANT MEETING INFORMATION** below).

b) The study data were collected in legacy Excel databases (raw data). The original analyses or study reports were based on raw data directly or legacy analysis data derived from the raw data. For this NDA, Chemo Research proposes to submit Clinical Data Interchange Standards Consortium (CDISC) compliant Study Data Tabulation Model (SDTM) data and Analysis Data Model (ADaM) data for the studies with complete raw data and data documents. For the studies with insufficient information for CDISC data conversion, the raw data will be converted as SAS datasets, and ADaM-like analysis datasets will be generated for statistical analysis. SAS transport files (xpt), define.xml or define.pdf and reviewer guides will be included for each of the studies.

Does the FDA agree with this approach?

FDA Response:

The approach appears to be acceptable. However, please ensure that all SAS datasets are in English. You may want to consider submitting the SAS datasets and a sample of SDTM and

ADaM datasets for at least the four controlled trials approximately a month prior to the NDA submission so that a preliminary assessment of the quality of the data can be made.

Discussion:

CHEMO stated they are prepared to submit the datasets for the studies the Agency has requested in these formats. The Agency inquired if it was possible for CHEMO to submit a sample/test dataset from one of the key efficacy studies for the Agency to review to ensure dataset quality. CHEMO stated they could do this but with a planned NDA submission forthcoming there was concern that CHEMO would not have sufficient time to respond to Agency feedback. The Agency stated that a preliminary assessment of the datasets by the Division's should take no more than two to three weeks. However, there is a separate Office that will be consulted to examine the datasets and the Agency would communicate their review time to CHEMO as quickly as possible.

c) An Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS) are planned. Integration of safety is expected however pooling of efficacy parameters may not be feasible due to the results from different dosages/populations/results. In this case an ISE is planned but data presentation is expected to be summarized tabulations (where feasible) in a side-by-side review. Does the Division agree with this approach?

FDA Response:

The approach appears to be acceptable.

Discussion: No further discussion was needed.

d) Based on the results of human Ether-a-go-go Related Gene (hERG) testing, observations of electrocardiogram (ECG) tracings, and the lack of cardiac toxicity reports in clinical use of BNZ, a tQT study was not conducted. Chemo Research submitted information at the 27 Apr 2016 End-of-Phase 2 meeting, as well as at the request of the QT Interdisciplinary Review Team on 8 July 2016, to support its request for a waiver of a tQT study. Does the FDA agree that these data are likely sufficient for a waiver of a tQT study as part of the Division's review of the planned NDA?

FDA Response:

We agree that the likelihood of benznidazole to significantly prolong QTc interval is low and a TQT study is not needed for the planned NDA.

Discussion: No further discussion was needed.

FDA Additional Comments:

Clinical Microbiology:

1. The different serological [indirect hemagglutination test, immunofluorescence assay, and different types of enzyme linked immunosorbent assays (ELISAs) including ELISAs

using F29, recombinant AT, and crude antigens] and molecular assays used in different studies are listed in Tables 16, 17, and 18 as well as in Appendix-B. From Table 14, it appears that a “*documentation of inter-laboratory standardization methods of quality assurance procedures*” will be included for some of the studies. However, it is unclear if validation reports for each of these assays for the proposed context of use, i.e., enrollment of patients in the clinical trial and measuring outcome, will be included in the NDA.

It will aid in our review if validation reports are provided for the different serological and molecular assays used for each of the 6 studies for which source data will be available and are included in the NDA submission: Sosa-Estani *et al.*, 1998; De Andrade *et al.*, 1996; DNDi-CD-PEDBZ-001; DNDi-CH-E1224-001; Molina *et al.*, 2014, Altchek *et al.*, 2014. In addition, validation reports for the different serological and molecular assays used in the studies by Viotti *et al.*, 2006, Fabbro *et al.*, 2007, Streiger *et al.*, 2004, and Morillo *et al.*, 2015 would also aid in our review. The validation reports should include details of the method as well as the performance characteristics of the assay in the laboratory where testing of clinical specimens was performed. The source of the information should be appropriately referenced and hyperlinked in the validation reports; name and address of the laboratory where testing was performed should be included. English translation of any supporting information that is published in a foreign language should be included.

Discussion:

CHEMO stated that there are some typographical errors in Table 14 and that other reports would be included in this section. The Agency stated that for all studies the following should be included: validation reports that include details of the method and performance characteristics of assay in the laboratory where testing of clinical specimens was performed. CHEMO stated that for the DNDi study, validation reports will be available whereas for some of the other studies e.g., Sosa-Estani and de Andrade studies, only laboratory manuals/methods are available. The Agency stated if a central laboratory was used for testing in any of the studies, the name of the laboratory should be specified.

The Agency stated that the type of information supporting the performance characteristics of the assay would depend on the context of use. Such information should include but not limited to data supporting sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), lower limit of detection, lower limit of quantitation, upper limit of quantitation, intra-laboratory and inter-laboratory variability, day to day variability, operator to operator variability, reproducibility, positive and negative controls used for testing as applicable.¹

CHEMO stated they are trying to do their best to provide the information, but it is possible that some of the requested information would not be available.

2. Details of all the parasitological methods used in different studies should be included.

¹ The following was not noted at the meeting. Stated here for Sponsor’s consideration:
If testing included any available World Health Organization standards as positive control, then such information should be included.

Discussion:

The Agency stated that for all of the 6 key studies CHEMO should provide the requested information. CHEMO stated that there is a mixture of what they have for each study and they would do their best to submit all requested information.

CHEMO stated that the details on parasitological methods will be provided.

3. Clarify if the results of serological and molecular testing of clinical specimens will be expressed qualitatively or quantitatively. We encourage you to share sham datasets with the Division, prior to submission of the NDA.

Discussion:

CHEMO stated they will provide both qualitative and quantitative data as applicable. For the de Andrade study only serology data is available; no PCR data are available. PCR data from this cohort is published in a study by Galvao (2003). However, the source data from this publication is not available; the publication will be included in the NDA submission.

The Agency inquired if CHEMO can provide a sample of the validation report. CHEMO inquired if the Agency would like this information submitted in eCTD format or in a PDF format. The Agency stated that they would like the validation report in PDF format and the patient level data (line listing) in an electronic format.

CHEMO stated that they will provide it before the NDA submission. CHEMO noted that they might be able to provide this information in a month. The Agency stated this would be acceptable, but asked to keep them updated.

Electronic submission:

From a technical standpoint (not content related), the structure and eCTD format for the planned NDA is acceptable. However, please see additional comments below:

1. There is no need to include Section numbering in your leaf title (e.g. 3.2.S.4.2.1.1 - Analytical Procedures (Residual Solvents, GC)).
2. For ease of review, all .pdf documents more than 5 pages long should have a table of contents (TOC), and proper and clear bookmarks and hyperlinks (including the Briefing Package, which was not bookmarked). For more information on submitting .pdf files, please refer to the PDF Specifications located here:
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163565.pdf>
3. Cross referenced information should be provided in m1.4.4. (cross reference to previously submitted information).
4. Make sure leaf titles of documents are clear and indicative of the content.

5. All module 4 literature references should reside in m4.3 ONLY and Module 5 Literature References in m5.4 ONLY.
6. Please note that Study Tagging Files (STF) files are required for submissions to the FDA when providing study information in modules 4 and 5 with the exception of module 4.3 Literature References, 5.2 Tabular Listing, 5.4 Literature References and 5.3.6 if the Periodic Report is a single PDF document. Each study should have an STF and all components regarding that study should be properly file tagged and placed under the study's STF, including case report forms (crfs). Case Report Forms need to be referenced in the appropriate study's STF to which they belong, organized by site as per the specifications and tagged as "case report form." Subject Data Listings (16.4) should be file tagged as "data-listing-dataset". For documents with no specific file tags, "study-report-body" or "legacy-clinical-study-report" file tag can be applied. Please refer to [The eCTD Backbone File Specification for Study Tagging Files 2.6.1 \(PDF - 149KB\) \(6/3/2008\)](#) - <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>

Discussion: No further discussion was needed.

Additional Discussion Points:

The Agency stated that two facilities were listed in this meeting package and inquired if there were any other facilities that will be involved in the commercial manufacture, packaging or testing of the drug product or the drug substance. CHEMO stated that there will be an additional facility responsible for microbiological testing. The Agency stated that CHEMO should submit a list of all facilities and their role in the NDA. The Agency asked about the source of the benzimidazole product which is now commercialized in Spain. CHEMO clarified that the product currently distributed in Spain is manufactured by ELEA (Argentina). Testing and release of product is done in (b) (4). Laboratory Liconsa in Spain is only responsible for the logistics of product distribution. The Agency requested complete and current physical addresses of facilities. CHEMO stated they could provide this information.

CHEMO then inquired if Agency had given any thought regarding the potential for an Advisory Committee meeting for this NDA. The Agency stated that it is premature to comment on the need for an Advisory Committee meeting, but NME NDAs are typically discussed at an Advisory Committee meeting.

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. The Agency agreed to the submission of patient source data from three additional publications (Fabbro, Streiger, Viotti) which could be accepted no later than 2 months after the NDA receipt date. For these studies

the Applicant agreed to summarize all patient data for Agency review at the time of NDA submission, but the source data for these additional publications, if obtained, would be submitted by 2 months post NDA submission.

The Applicant was advised to prominently identify each submission containing the late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

NDA NUMBER: LATE COMPONENT - CLINICAL

- The Agency indicated the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER’s standard format for electronic regulatory submissions. Beginning **May 5, 2017**, the following submission types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

SECURE EMAIL COMMUNICATIONS

Secure email is **required** for all email communications from FDA to applicants when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), applicants must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

505(b)(2) REGULATORY PATHWAY

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 draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.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 that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval, in part, 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, in part, 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 or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g., trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the 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 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. 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.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication X</i>
<i>3. Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section XXX</i>
<i>4.</i>	

Please 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 a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to 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 Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

Please be advised that the Agency does not make exclusivity determinations pursuant to sections 505(c)(3)(E) and (j)(5)(F) of the Federal Food, Drug, and Cosmetic Act, and 21 CFR 314.108, until after approval of an NDA. As described at 314.50(j), an applicant should include in its NDA a description of the exclusivity to which the applicant believes it is entitled. FDA will consider the applicant’s assertions regarding exclusivity in the review of the application. Please also note that the New Molecular Entity (NME) determination for an application is distinct from and independent of the New Chemical Entity (NCE) determination and any related exclusivity determinations.

FDA has made a preliminary determination that the application for this product would be reviewed as a new molecular entity (NME) and therefore subject to the Program, under PDUFA V. Please note that this is a preliminary determination, based on information available to FDA at this time, and will be re-evaluated at the time your application is submitted. This determination is based on our understanding of the active moiety (21 CFR 314.108(a)) and whether another marketing application containing the same active moiety is approved or marketed. Please also note that the NME determination for an application is distinct from and independent of the new chemical entity (NCE) determination and any related exclusivity determinations, which are made after approval of an NDA.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

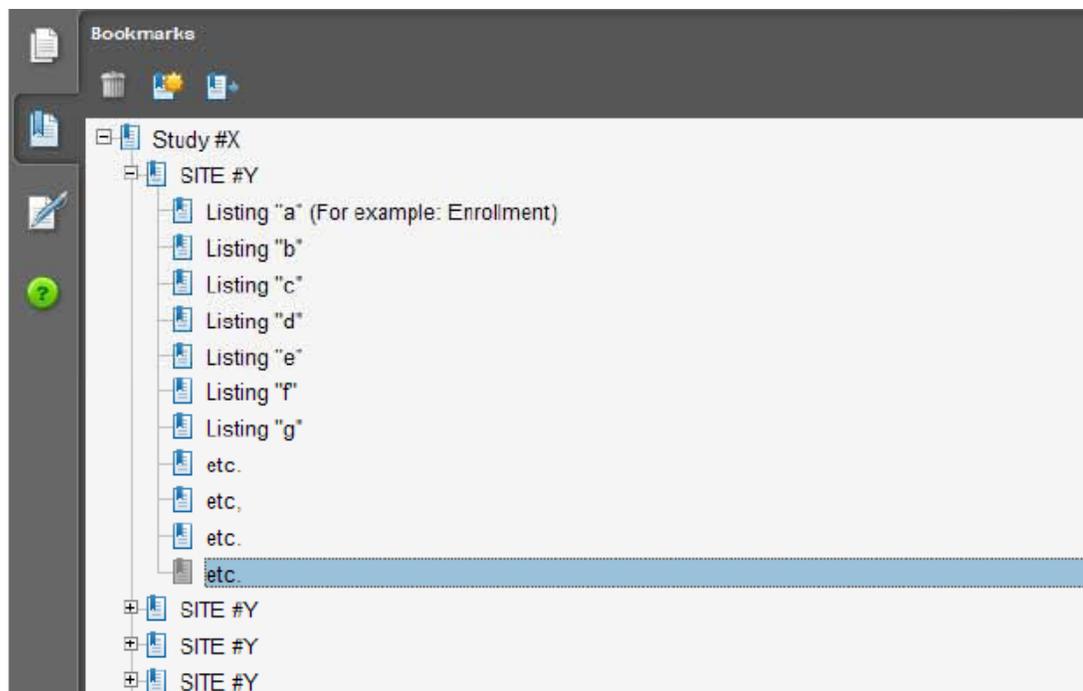
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records,

- IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
- b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
 5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item²	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

² Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

4.0 ISSUES REQUIRING FURTHER DISCUSSION

- CHEMO will provide a sample data set for Agency review.
- CHEMO will information on facilities involved in manufacturing and testing benznidazole.
- CHEMO to provide sample of method validation reports per request from the Agency clinical microbiology team.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Issue Meeting Minutes to CHEMO	FDA	October 28, 2016
Provide time line for review of sample data set	FDA	Within 1 week of meeting
Provide sample data set for FDA review	CHEMO	Pending FDA response, but within 1 month of NDA submission
Provide information on facilities involved in manufacturing and testing of benznidazole	CHEMO	Within 1 month of meeting date.
Provide Information on method validation reports	CHEMO	By the end of October 2016

6.0 ATTACHMENTS AND HANDOUTS

FDA September 26, 2016 Preliminary Meeting Responses

From: DiBernardo, Gregory
To: [REDACTED] (b) (4)
Cc:
Subject: FDA Communication: PIND 118976-benznidazole-CHEMO-FDA Preliminary Meeting Responses
Date: Monday, September 26, 2016 9:06:00 PM
Attachments: [FINAL FDA Preliminary Meeting Response for 09.30.16 Meeting.pdf](#)
Importance: High

Hello [REDACTED] (b) (4),

I am proving the FDA Preliminary Meeting Comments for the meeting scheduled for September 30, 2016, regarding PIND 118976. Please be aware there will be no paper/hardcopy communication to follow this email communication.

Following your review of this information, please let me know if you plan to reduce the number of questions for discussion, change the format of the meeting to a teleconference, or cancel the scheduled meeting.

Please let me know if you have questions.

Thank you,

Gregory F. DiBernardo

Regulatory Project Manager
FDA/CDER/OND/OAP/Division of Anti-Infective Products
10903 New Hampshire Avenue
Building 22, Room 6223
Silver Spring, MD 20993
Telephone: (301) 796-4063



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

COMMUNICATION SHEET

DATE: September 26, 2016

To: (b) (4)	From: Gregory F. DiBernardo Regulatory Project Manager
Company: CHEMO Research c/o (b) (4) (b) (4)	Division of Anti-Infective Products (DAIP)
Fax number: Communication sent via E-mail	Fax number: (301) 796-9882
Phone number: (b) (4)	Phone number: (301) 796-4063
E-mail: (b) (4) Cc: (b) (4) (b) (4)	
Subject: PIND 118976, Benznidazole	

Total no. of pages including cover: 6

Comments:

FDA Preliminary Comments to questions outlined in your August 30, 2016, briefing document in preparation for the September 30, 2016, meeting.

Confirm receipt of this communication at: gregory.dibernardo@fda.hhs.gov

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-1400. Thank you.

Pre-Investigational New Drug Application (PIND) Number: 118976

Drug Name: Benznidazole Tablets, 12.5 mg and 100 mg

Re: FDA Preliminary Meeting Responses

This document provides our preliminary responses to the questions outlined in your briefing document dated August 30, 2016, and additional comments in preparation for the meeting scheduled for September 30, 2016, at 11:00 A.M. between representatives for CHEMO Research (CHEMO) and the Division of Anti-Infective Products (DAIP). We are sharing these in advance of the meeting to promote a collaborative and successful discussion. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda for the meeting, again please contact the RPM. It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions.

9.1 Chemistry, Manufacturing, and Controls

Does the FDA agree with the content, structure, and electronic Common Technical Document (eCTD) format for presenting Chemistry Manufacturing and Controls (CMC) information provided for Module 2.3 and Module 3?

FDA Response:

The content and structure for Module 2.3 and Module 3 in eCTD format appear to be acceptable. For more information for submissions in electronic format, refer to FDA Guidance for Industry; Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions using the eCTD Specifications. Also, please refer to the FDA Additional Comments, below.

We note that drug product registration batches are manufactured with the drug substance from (b) (4) and drug product batches used in development were manufactured with the drug substance from (b) (4). We remind you of the Agency recommendations regarding the bridging of the two API sources and other CMC recommendations for your drug substance and the drug product provided in the correspondences dated May 11, and May 27, 2016.

9.2 Nonclinical

Does the FDA agree with the content, structure, and eCTD format for presenting nonclinical information provided for Modules 2.4/2.6 and Module 4?

FDA Response:

Pharmacology/Toxicology:

The general content, structure, and eCTD format for the nonclinical safety pharmacology, pharmacokinetic, and toxicology information to be provided in Modules 2.4/2.6 and Module 4 as summarized Tables 9 and 10 of the Meeting Package are acceptable, except some of the studies previously included in the March 24, 2016, submission are not included. Please include the studies listed below. In Module 4, all of the non-literature reports listed in Table 9 should be included in full study reports and all of the literature reports listed in Table 10 should be included in their entirety including English translations when necessary.

1. DNDi. (2009). Study report no. CDCO_DNDI_09_032_PK: Pharmacokinetics of EPL-BS0063 in male Sprague Dawley rats following IV and oral administration.
2. DNDi. (2009). Study report no. CDCO_DNDI_09_029_DDI: Assessment of potential CYP3A4 inhibition by twenty four compounds using a substrate specific interaction approach in human liver microsomes.

Clinical Microbiology:

It appears from Table 9 that one microbiology study “A potential for development of resistance and activity against different lineages of *T. cruzi*” will be included in Module 4.2.3.7.7 and five studies will be included in Module 4.2.1.1. However, some of the studies which were listed in submission dated March 24, 2016, to support *in vitro* and *in vivo* activity of benznidazole against *T. cruzi* were not listed in this submission. It will aid in our review if all microbiology studies, published or unpublished that include details of the experimental design and results, are included in Module 4. English translation of any of the studies that are published in a foreign language should be included. All microbiology studies should be summarized under the subheadings that include mechanism of action, activity *in vitro* and in animal models, as well as drug resistance in Module 2.

9.3 Clinical

a) Six clinical studies were conducted between 1991 and 2015 by various investigators. Chemo Research has been able to gain access to study related source information, including certain patient-level data. Does the Division consider the data that Chemo Research is proposing to submit sufficient for the Division’s review of a 505(b)(2) NDA for BNZ for the treatment of Chagas disease?

FDA Response:

The source data from the six studies listed seem to be adequate for the review of an NDA. Data that correlate clinical outcomes to assay results will be critical. If, in the studies conducted in the adult population, such as the Molina study of benznidazole vs. posaconazole and the Morillo study (BENEFIT), some serology data were collected as a secondary endpoint, it will be helpful for the review. In the NDA please provide a justification to link serological responses and clinical outcomes.

It is highly desirable that you provide as much source information as possible from studies that correlate clinical outcomes with PCR assays or serological responses in children and/or adults. For example, source data from the Fabbro 2007, Streiger 2004, and the Viotti 2006 studies could be helpful to support a bridge between treatment, serological responses and clinical outcomes. These studies provide data on untreated patients, and will help to understand outcomes in untreated disease. As discussed previously, data on natural history of untreated disease in neonates and children ages 0 to 6 years old will be essential (b) (4) in that age group. The therapeutic effect needs to be demonstrated with a comparison of outcomes of treated patients to the outcomes of those with untreated disease. If you believe that efficacy in children under 6 years of age can be extrapolated from a finding of efficacy in older children, you will need to show that the course of the disease (persistent serological positivity, clinical phases of the disease) and the effects of the drug are sufficiently similar in both groups.

b) The study data were collected in legacy Excel databases (raw data). The original analyses or study reports were based on raw data directly or legacy analysis data derived from the raw data. For this NDA, Chemo Research proposes to submit Clinical Data Interchange Standards Consortium (CDISC) compliant Study Data Tabulation Model (SDTM) data and Analysis Data Model (ADaM) data for the studies with complete raw data and data documents. For the studies with insufficient information for CDISC data conversion, the raw data will be converted as SAS datasets, and ADaM like analysis datasets will be generated for statistical analysis. SAS transport files (xpt), define.xml or define.pdf and reviewer guides will be included for each of the studies.

Does the FDA agree with this approach?

FDA Response:

The approach appears to be acceptable. However, please ensure that all SAS datasets are in English. You may want to consider submitting the SAS datasets and a sample of SDTM and ADaM datasets for at least the four controlled trials approximately a month prior to the NDA submission so that a preliminary assessment of the quality of the data can be made.

c) An Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS) are planned. Integration of safety is expected however pooling of efficacy parameters may not be feasible due to the results from different dosages/populations/results. In this case an ISE is planned but data presentation is expected to be summarized tabulations (where feasible) in a side-by-side review. Does the Division agree with this approach?

FDA Response:

The approach appears to be acceptable.

d) Based on the results of human Ether-a-go-go Related Gene (hERG) testing, observations of electrocardiogram (ECG) tracings, and the lack of cardiac toxicity reports in clinical use of BNZ, a tQT study was not conducted. Chemo Research submitted information at the 27 Apr 2016 End-of-Phase 2 meeting, as well as at the request of the QT Interdisciplinary Review Team on 8 July 2016, to support its request for a waiver of a tQT study. Does the FDA agree that these data are likely sufficient for a waiver of a tQT study as part of the Division's review of the planned NDA?

FDA Response:

We agree that the likelihood of benznidazole to significantly prolong QTc interval is low and a TQT study is not needed for the planned NDA.

FDA Additional Comments:

Clinical Microbiology:

1. The different serological [indirect hemagglutination test, immunofluorescence assay, and different types of enzyme linked immunosorbent assays (ELISAs) including ELISAs using F29, recombinant AT, and crude antigens] and molecular assays used in different studies are listed in Tables 16, 17, and 18 as well as in Appendix-B. From Table 14, it appears that a “*documentation of inter-laboratory standardization methods of quality assurance procedures*” will be included for some of the studies. However, it is unclear if validation reports for each of these assays for the proposed context of use, i.e., enrollment of patients in the clinical trial and measuring outcome, will be included in the NDA.

It will aid in our review if validation reports are provided for the different serological and molecular assays used for each of the 6 studies for which source data will be available and are included in the NDA submission: Sosa-Estani *et al.*, 1998; De Andrade *et al.*, 1996; DNDi-CD-PEDBZ-001; DNDi-CH-E1224-001; Molina *et al.*, 2014, Altcheh *et al.*, 2014. In addition, validation reports for the different serological and molecular assays used in the studies by Viotti *et al.*, 2006, Fabbro *et al.*, 2007, Streiger *et al.*, 2004, and Morillo *et al.*, 2015 would also aid in our review. The validation reports should include details of the method as well as the performance characteristics of the assay in the laboratory where testing of clinical specimens was performed. The source of the information should be appropriately referenced and hyperlinked in the validation reports; name and address of the laboratory where testing was performed should be included. English translation of any supporting information that is published in a foreign language should be included.

2. Details of all the parasitological methods used in different studies should be included.

3. Clarify if the results of serological and molecular testing of clinical specimens will be expressed qualitatively or quantitatively. We encourage you to share sham datasets with the Division, prior to submission of the NDA.

Electronic submission:

From a technical standpoint (not content related), the structure and eCTD format for the planned NDA is acceptable. However, please see additional comments below:

1. There is no need to include Section numbering in your leaf title (e.g. 3.2.S.4.2.1.1 - Analytical Procedures (Residual Solvents, GC)).
2. For ease of review, all .pdf documents more than 5 pages long should have a table of contents (TOC), and proper and clear bookmarks and hyperlinks (including the Briefing Package, which was not bookmarked). For more information on submitting .pdf files, please refer to the PDF Specifications located here:
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163565.pdf>
3. Cross reference information should be provided in m1.4.4. (cross reference to previously submitted information).
4. Make sure leaf titles of documents are clear and indicative of the content.
5. All module 4 literature references should reside in m4.3 ONLY and Module 5 Literature References in m5.4 ONLY.
6. Please note that Study Tagging Files (STF) files are required for submissions to the FDA when providing study information in modules 4 and 5 with the exception of module 4.3 Literature References, 5.2 Tabular Listing, 5.4 Literature References and 5.3.6 if the Periodic Report is a single PDF document. Each study should have an STF and all components regarding that study should be properly file tagged and placed under the study's STF, including case report forms (crfs). Case Report Forms need to be referenced in the appropriate study's STF to which they belong, organized by site as per the specifications and tagged as "case report form." Subject Data Listings (16.4) should be file tagged as "data-listing-dataset". For documents with no specific file tags, "study-report-body" or "legacy-clinical-study-report" file tag can be applied. Please refer to [The eCTD Backbone File Specification for Study Tagging Files 2.6.1 \(PDF - 149KB\)](http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf) (6/3/2008) -
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>

If you have any questions regarding this communication, please contact Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

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

/s/

SUMATHI NAMBIAR
10/28/2016

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 209570

LATE-CYCLE MEETING MINUTES

Chemo Research, S.L.
c/o Exeltis
Attention: Sandy S. Suh, Pharm.D.
Head, Regulatory Affairs (R&D)
180 Park Avenue, Suite 101
Florham Park, NJ 07928

Dear Dr. Suh:

Please refer to your New Drug Application (NDA) dated December 29, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Benznidazole Tablet 100 mg and 12.5 mg.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on June 27, 2017.

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

If you have any questions, call Mr. Gregory DiBernardo, Regulatory Project Manager at (301) 796-4063.

Sincerely,

{See appended electronic signature page}

Thomas D. Smith, M.D.
Cross Discipline Team Leader
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: June 27, 2017, 3:00 PM to 4:00 PM ET
Meeting Location: White Oak Campus, Building 22, Room 1309
Application Number: NDA 209570
Product Name: Benznidazole Tablets
Applicant Name: Chemo Research, S.L.
Meeting Chair: Thomas D. Smith, M.D.
Meeting Recorder: Gregory DiBernardo

FDA ATTENDEES

Office of Antimicrobial Products

Edward Cox, M.D., M.P.H. Director
John J. Farley, M.D., M.P.H. Deputy Director

Division of Anti-Infective Products

Sumathi Nambiar, M.D., M.P.H. Director
Dmitri Iarikov, M.D., Ph.D. Acting Deputy Director
Joseph Toerner, M.D., M.P.H. Deputy Director for Safety
Thomas Smith, M.D. Cross Discipline Team Leader
Maria Allende, M.D. Clinical Reviewer
Avery Goodwin, Ph.D. Acting Clinical Microbiology Team Leader
Shukal Bala, Ph.D. Clinical Microbiology Reviewer
Owen McMaster, Ph.D. Acting NonClinical Team Leader
James Wild, Ph.D. NonClinical Reviewer
Abimbola Adebowale, Ph.D. Associate Director for Labeling
Maureen Dillon-Parker Chief, Project Management Staff
Gregory F. DiBernardo Regulatory Project Manager

Division of Clinical Pharmacology IV

John Lazor, Pharm.D. Director
Yongheng (Eric) Zhang, Ph.D. Clinical Pharmacology Reviewer
Abhay Joshi, Ph.D. Clinical Pharmacology Reviewer

Division of Pharmacometrics

Jeffry Florian, Ph.D. Lead Pharmacologist

Division of Biometrics IV

Karen Higgins, Sc.D.
Janelle Charles, Ph.D.

Biostatistics Team Leader
Biostatistics Reviewer

Office of Pharmaceutical Quality

Dorota M. Matecka, Ph.D.
Yong Wang, Ph.D.

Product Quality Team Leader
Product Quality (Drug Product) Reviewer

Office of Surveillance and Epidemiology

Elizabeth Everhart
Mingfeng Zhang
Sevan Kolejian, Pharm.D.
Janet Higgins

DRISK Team Leader
DEPI-II Epidemiology Reviewer
DMEPA Safety Reviewer
Senior Regulatory Project Manager

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APPLICANT ATTENDEES

Chemo Research, S.L.

Enrico Colli, M.D.

Chief Scientific Officer

 (b) (4)

Exeltis USA, Inc.

Sandy Suh, Pharm.D.

Head, Regulatory Affairs

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1.0 BACKGROUND

NDA 209570 was submitted on December 29, 2016, for Benznidazole Tablets, 100 mg and 12.5 mg.

Proposed indication: Treatment of Chagas disease

PDUFA goal date: August 29, 2017

FDA issued a Background Package in preparation for this meeting on June 16, 2017.

2.0 DISCUSSION

1. Introductory Comments

After introductions, the Division explained the purpose and objectives of the Late-Cycle Meeting and informed the Sponsor (Chemo) that the application has not yet been fully reviewed by the signatory authority and Cross-Discipline Team Leader (CDTL); therefore, the final regulatory decision for the application will not be addressed at the meeting.

2. Discussion of Substantive Review Issues

Clinical:

[REDACTED] (b) (4)

In children with indeterminate infection, we believe that the appropriate clinical endpoint is serologic cure. We agree that the data submitted provide substantial evidence of efficacy in this population with an endpoint (seroreversion on nonconventional serologic assays) reasonably likely to predict clinical benefit. Thus, we are considering a Subpart H approval. We would like to discuss a feasible design for the required confirmatory study (see item 6 below). We believe there are adequate exposure data to extrapolate efficacy down to age 2 years. We have provided dosing recommendations for children ages 2-12 years; [REDACTED] (b) (4)

Discussion:

Chemo stated that it agreed with FDA to focus the current NDA on the pediatric population 2-12 years of age. [REDACTED] (b) (4)

[REDACTED] (b) (4)

3. Discussion of Minor Review Issues

Dosing recommendation for pediatric patients 2-12 years of age: (b) (4)

(b) (4) the Division recommends BNZ dosing of 5-8 mg/kg/day (administered as BID approximately 12 hours apart) in pediatric patients 2 - 12 years of age. This recommendation is based on our analysis of the two pediatric efficacy studies: Sosa-Estani et al 1998 (5 mg/kg/day) and De Andrade et al 1996 (7.5 mg/kg/day), the pediatric study conducted by Altcheh et al 2014 (5-8 mg/kg/day), and the provided clinical pharmacology studies (LPRI 747/101 and LPRI 747/102) bridging the to-be-marketed formulation with the Radanil formulation used in the aforementioned three clinical studies.

Discussion:

FDA stated that they recommend benznidazole dosing of 5-8 mg/kg/day (administered as BID approximately 12 hours apart) in pediatric patients 2 - 12 years of age. FDA also proposed to include a dosing table (listed below under section #6) in labeling. Chemo stated that they understood the FDA's rationale for the proposed benznidazole dosing in pediatric patients 2 - 12 years of age and agree to include the proposed dosing table in the prescribing information.

4. Information Requests (IRs)

The following are pending:

- May 25, 2017, request for safety information for the product label, to replace the current Table 1.
- May 24, 2017, from DPMH, requesting data on pregnancy, lactation, and effects on female and male fertility to justify the PLLR sections of the label. The response is currently under review.
- April 14, 2017, requesting whether seroreversion observed in the follow-up of the Sosa-Estani study (published in the Sosa-Estani 2002 article) was confirmed with one or more conventional serological assays. (Note: partial response May 1, 2017),
- April 3, 2107, nonclinical request.
- June 5, 2017, product quality request.
- June 15, 2017, labeling with DMEPA carton/container edits.

Discussion: The Sponsor provided an email on June 26, 2017, with updates for these pending IRs (attached); therefore, there was no further discussion of these topics.

5. Postmarketing Requirements/Postmarketing Commitments

Postmarketing Requirements

- A (b) (4) study (b) (4)
(b) (4), single-arm (b) (4) historical control (b) (4)
(b) (4) PK (b) (4)
(b) (4)
- ADME/mass balance study in humans
- Male fertility study in rats (agreed to in the End of Phase 2 meeting on April 27, 2016)

Discussion:

(b) (4)

6. Major Labeling Issues

Once an agreement is reached on dosing, we recommend that you consider including the following table in the product labeling to provide guidance to physicians and patients.

Body weight range (kg)	BID Dose (mg)*
< 15	50
15 - < 20	62.5
20 - < 30	75
30 - < 40	100
40 - < 60	150
> 60	200

* The dose should be administered twice a day approximately 12 hours apart for 60 days

We plan to issue a complete draft label in July, 2017.

Discussion:

FDA stated that the proposed table would be useful for prescribers and recommended that it should be included in labeling. Chemo agreed that they would include the proposed table in the prescribing information.

FDA stated that it intends to provide Chemo draft labeling in July, 2017, for review and comments.

Post-Meeting note: FDA plans to issue draft labeling in early August, 2017.

7. Review Plans

- Internal labeling discussions are ongoing
- The Division plans to complete reviews and take action by the August 29, 2017, PDUFA goal date.

Discussion: No further discussion.

8. Wrap-up

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

ATTACHMENT – Response to IRs received June 26, 2017

From: [Sandy Suh](#)
To: [DiBernardo, Gregory](#)
Subject: NDA 209570 BNZ: outstanding IR responses
Date: Monday, June 26, 2017 5:06:13 PM

Hi Gregory,

The table below includes all of the IR items mentioned in the Late Cycle Meeting Background Package (6 bullets on Page 5). In addition, there were 4 IR requests not mentioned but still pending.

These have been included. And lastly, the request for clarification of the Financial Information (received today, 26Jun) is also included.

In sum, 11 items are listed (6 mentioned in the Late Cycle agenda, 4 items that were also pending, and one fresh clarification request).

Kindest regards,

sandy

NDA 209570

Benznidazole

	FDA IR Date and Topic	Sponsor NDA Submission Location or Current Status
1.	IR from May 25, 2017, requesting safety information for the product label, to replace the current Table 1.	Internal completion by end of this week; anticipated submission to/arrival at FDA next week.
2.	IR from May 24, 2017, from DPMH, requesting data on pregnancy, lactation, and effects on female and male fertility to justify the PLLR sections of the label. The response is currently under review.	Response provided in (0024) cover letter dated 13Jun. Response currently under FDA review.
3.	IR from April 14, 2017, (partial response May 1, 2017), requesting whether seroreversion observed in the follow-up of the Sosa Estani study (published in the Sosa Estani 2002 article) was confirmed with one or more conventional serological assays.	Partial response (0016) cover letter dated 28Apr mentions additional information will be provided if received. As of today (26Jun), no further information was received and additional information is not expected.
4.	April 3, 2017, nonclinical IR.	Response (0016) cover letter dated 28Apr.
5.	June 5, 2017, product quality IR.	Response (0025) cover letter dated 19Jun.
6.	June 15, 2017, Labeling IR with DMEPA carton/container edits	Internal completion by end of this week; anticipated submission to/arrival at FDA next week.

7.	16May clin micro	Internally completed (submission to/arrival at FDA this week).
8.	16May biostat	Internally completed (submission to/arrival at FDA this week).
9.	26May labeling text	Internal completion by end of this week; anticipated submission to/arrival at FDA next week.
10.	16Jun withdrawal of proprietary	Withdrawal and resubmission of proprietary name completion pending; anticipated by end of this week with submission to/arrival at FDA next week.
11.	26Jun clarification of Financial Disclosure	Response provided in (0007) cover letter dated 24Feb

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

/s/

THOMAS D SMITH
07/26/2017