CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201820Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 201820 SUPPL # HFD #

Trade Name Bethkis

Generic Name tobramycin 300 mg/4mL inhalation solution

Applicant Name Chiesi Pharmaceuticals, Inc.

Approval Date, If Known 10/12/12

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES X

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

505(b)(2)

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

YES X NO ☐

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

N/A

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

N/A

d) Did the applicant request exclusivity?

YES ☐ NO X

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

N/A

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

NO X

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

No

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

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

NO X

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES X

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

NDA#	NDA 50-753	TOBI (tobramycin) Inhalation Solution USP
NDA#	NDA 50-555	Tobrex Oint
	NDA 50-789	Tobramycin Sulfate Injection
NDA#	NDA 50-541	Tobrex Opth Solution

2. Combination product.

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

NO X

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical

investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES X

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

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

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

YES X

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

N/A

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

YES X

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

NO X

If yes, explain:

N/A

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

NO X

If yes, explain: N/A

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

1. CT01 was a randomized, double-blind, placebo-controlled trial of 28 days of CHF 1538 or placebo with a 28-day follow-up period.

2. CT02 was a randomized, double-blind, placebo controlled trial of three cycles (28 days on-/28 days off-treatment) of CHF1538 or placebo.

3. CT03 was a randomized, open-label, comparative trial of CHF1538 or TOBI given for 28 days with a 28-day follow-up period.

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

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

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

Investigation #1	YES ☐	NO X
Investigation #2	YES ☐	NO X
Investigation #3	YES ☐	NO X

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

N/A

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

Investigation #1 YES ☐ NO X

Investigation #2 YES ☐ NO X

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

N/A

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

1. CT01 was a randomized, double-blind, placebo-controlled trial of 28 days of CHF 1538 or placebo with a 28-day follow-up period.

2. CT02 was a randomized, double-blind, placebo controlled trial of three cycles (28 days on-/28 days off-treatment) of CHF1538 or placebo.

3. CT03 was a randomized, open-label, comparative trial of CHF1538 or TOBI given for 28 days with a 28-day follow-up period.

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

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

Investigation #1
IND # 72,068 YES X NO ☐
Explain:
N/A

Investigation #2

IND # 72,068 YES X NO ☐
Explain:
N/A

Investigation #3

IND # 72,068 YES X NO ☐
Explain:
N/A

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

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

YES ☐ NO X

If yes, explain:

N/A

Name of person completing form: Carmen DeBellas
Title: Project Manager
Date: September 14, 2012

Name of Office/Division Director signing form: Dr. John Farley, MD, MPH
Title: Acting Director

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

/s/

CARMEN L DEBELLAS
10/12/2012

JOHN J FARLEY
10/12/2012

3. DEBARMENT CERTIFICATION

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

Erika B Panico

Erika Panico

Vice President and Managing Director

Chiesi Pharmaceuticals Inc.

24 Sep 10

Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 201820 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Bethkis 300 mg/4mL Inhalation Solution Established/Proper Name: tobramycin Dosage Form: Inhalation solution		Applicant: Chiesi Pharmaceuticals Agent for Applicant (if applicable):
RPM: Carmen DeBellas		Division: Anti-Infective Products

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☐ 505(b)(1) X 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

NDA 50-753 TOBI (tobramycin) 400 mg/5mL Inhalation Solution

Provide a brief explanation of how this product is different from the listed drug.

The applicant is request a new concentration 300 mg/4mL Tobramycin Solution. The approved TOBI is 300 mg/5mL.

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
X This application relies on (explain) Phase 1 Bioavailability and Pharmacokinetic studies

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

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.

❖ Actions	
• Proposed action • User Fee Goal Date is October 12, 2012	X AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None Complete Response August 25, 2012

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

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

❖ 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 ____	☐ Received
❖ Application Characteristics [3]	

Review priority: X Standard ☐ Priority
Chemical classification (new NDAs only): 5S

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation

☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ 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

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

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	X Yes ☐ No
• Press Office notified of action (by OEP)	X Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	X None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[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. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	X No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	X No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	X No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	X No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	X No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	X No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	**X** Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) **X** Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) **X** Verified

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

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

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? — **X** Yes ☐ No

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

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

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? — ☐ Yes ☐ No

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

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

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? — ☐ Yes ☐ No

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

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

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? — ☐ Yes X No

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

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

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

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist[4]	10/12/12
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	X Included
Documentation of consent/non-consent by officers/employees	X Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Approval 10/12/12 Complete Response 8/25/11
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	September 11 ,2012
• Original applicant-proposed labeling	10/25/10
• Example of class labeling, if applicable	10/25/10

[4] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide X Patient Package Insert X Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	10/2/12
• Original applicant-proposed labeling	4/12/12
• Example of class labeling, if applicable	N/A
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	7/23/12
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	AP 8/3/12 UA 4/27/12 UA 4//29/11 UA 1/25/11
❖ Labeling reviews *(indicate dates of reviews and meetings)*	X DMEPA 9/11/12 X OSE 7/1/11 & 1/25/11 X ODPD (DDMAC) 9/26/12 X DMPP 10/1/12 X DCDP 10/2/12
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	1/20/11 8/1/11 8/31/12
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	X Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes X No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes X No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC If PeRC review not necessary, explain: Pediatric Indication all groups studied or studies waived. • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	X Verified, statement is acceptable
❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	**1/7/11**
❖ Internal memoranda, telecons, etc.	N/A
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	X No meeting
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	12/16/11
• Pre-NDA/BLA meeting *(indicate date of mtg)*	7/22/09
• EOP2 meeting *(indicate date of mtg)*	X No meeting
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	N/A
❖ Advisory Committee Meeting(s)	X No AC meeting
• Date(s) of Meeting(s)	N/A
• 48-hour alert or minutes, if available *(do not include transcript)*	N/A
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	X None
Division Director Summary Review *(indicate date for each review)*	10/12/12 & 8/25/11
Cross-Discipline Team Leader Review *(indicate date for each review)*	10/12/12 & 8/24/11
PMR/PMC Development Templates *(indicate total number)*	1 PMR
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	See Cross Discipline Reivew
• Clinical review(s) *(indicate date for each review)*	8/19/11 & 10/2/12
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	X None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See Clinical Review 8/9/11 Page 17
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	Division Pulmonary and Allergy Products 4/5/11 Regulatory Device Consult 10/11/12 & 6/10/11
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	X Not applicable

[6] Filing reviews should be filed with the discipline reviews.

❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	X None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	7/14/11
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	X None
Clinical Microbiology Review(s) *(indicate date for each review)*	6/21/12, 8/18/11 & 6/1/11
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	X None
Statistical Team Leader Review(s) *(indicate date for each review)*	X None
Statistical Review(s) *(indicate date for each review)*	10/2/12 & 6/23/11
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	X None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	X None
Clinical Pharmacology review(s) *(indicate date for each review)*	6/30/11
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	X None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	X None
• Supervisory Review(s) *(indicate date for each review)*	X None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	5/1/12 & 7/19/11
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	X None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	X No carc
❖ ECAC/CAC report/memo of meeting	X None
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	X None requested

Product Quality ☐ None	
Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	X None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	X None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	8/31/12, 8/24/11 & 6/24/11
❖ Microbiology Reviews X NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	6/20/12 & 7/8/11
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See CMC Review
☐ Review & FONSI *(indicate date of review)*	See CMC Review
☐ Review & Environmental Impact Statement *(indicate date of each review)*	See CMC Review
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: See CMC Review **X** Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: N/A ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	**X** Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[7] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

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

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

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

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

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

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

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

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

From: DeBellas, Carmen
Sent: Monday, July 16, 2012 3:03 PM
To: 'Erika Panico'
Subject: Statistics Request

Hi Erika,

Can you provide the information or where we can locate the information in the request below?

Please provide the formula and explicit derivation of adjusted pulmonary function tests (PFTs) in a sample of patients from Study CT02 (i.e. twenty patients) with discordant database and spirometry values of PFT determinants (height, FEV1, FVC, etc.).

Thanks,
Carmen

Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

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/s/

CARMEN L DEBELLAS
07/18/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

IND 72,068

Chiesi Pharmaceuticals, Inc.
Attention: Erica Panico, RAC (US)
9605 Medical Center Drive
Suite 380
Rockville, MD 20850

Dear Ms. Panico:

Please refer to your Investigational New Drug Application (IND) for CHF 1538 (tobramycin 300mg/4mL Inhalation Solution). We also refer to the meeting between representatives of your firm and the FDA on July 22, 2009. The purpose of the meeting was to discuss your future marketing application for CHF 1538.

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

If you have any questions, call J. Christopher Davi, MS, Senior Regulatory Project Manager at (301) 796-0702.

Sincerely,

{See appended electronic signature page}

Katherine A. Laessig
Deputy Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosures: Minutes from meeting
Pre-meeting comments dated July 21, 2009

CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF TELECONFERENCE

MEETING DATE: July 22, 2009
MEETING TIME: 10:30 to 11:30 AM, EST

APPLICATION (DRUG): IND 72,068

SPONSOR: Chiesi Pharmaceuticals, Inc. – CHF 1538 (Tobramycin 300 mg/4mL Inhalation Solution)

TYPE OF MEETING: Pre-NDA
MEETING CHAIR: Katherine A. Laessig, MD, Deputy Director
MEETING RECORDER: J. Christopher Davi, MS, Regulatory Project Manager

FDA PARTICIPANTS, Division of Anti-Infective and Ophthalmology Products (DAIOP):
Katherine A. Laessig, MD, Deputy Director
John J. Alexander, MD, MPH, Medical Team Leader
Menfo Imoisili, MD, MPH, Medical Reviewer
Nasim Moledina, MD, Medical Reviewer
Charles Bonapace, PharmD, Clinical Pharmacology Team Leader
Yongheng Zhang, Ph.D., Clinical Pharmacology Reviewer
Thamban Valappil, PhD, Team Leader, Biometrics
Chris Kadoorie, PhD, Biostatistics Reviewer
Wendelyn Schmidt, PhD, Preclinical Pharmacology Team Leader
Amy Ellis, PhD, Preclinical Pharmacology Reviewer
Dave Roeder, MS, Associate Director of Regulatory Affairs, OAP
J. Christopher Davi, MS, Regulatory Project Manager

SPONSOR PARTICIPANTS, Chiesi Pharmaceuticals, Inc.:
Steven Linberg, PhD, Managing Director
Helen Cicirello, MD, Medical Director
Erica Panico, RAC, Associate Director, Regulatory Affairs
Susan Gamble, PhD, Assistant Director, Regulatory Affairs
Karen Wagner, Clinical Trials Assistant
Marco Zibellini, MD, Head of Internal Medicine Unit
(b) (4) PhD, Toxicology Consultant

MEETING OBJECTIVE:

To discuss the future marketing application for CHF 1538.

SUMMARY OF DISCUSSION:

The Division of Anti-Infective and Ophthalmology Products (DAIOP) granted the Sponsor a pre-NDA meeting to discuss their future marketing application for CHF 1538. DAIOP provided preliminary comments to the Sponsor on July 21, 2009 (appended). Discussion points generated from the preliminary comments are provided as follows:

- The Sponsor noted that the ICHQ3B guidance document does not cover fermentation products and asked whether there were any similar guidance documents that did. The Division suggested that this matter be discussed at the CMC meeting scheduled for the next day, but indicated that from the nonclinical pharmacology/toxicology standpoint, the Division would not recommend that the product CHF 1538 be held to a higher standard than those discussed in guidance documents covering impurities for similar products. The Sponsor's proposal for qualifying impurities that might be identified using the HPLC methodology appear reasonable.

- The Sponsor informed the Division that they would provide a list of impurites and proposed limits to the Division. Additionally, they will identify which substances have and have not been qualified in previous studies, and provide specific plans for qualification (if needed). The Division will provide the Sponsor with feedback on this list and on their plans for qualification. The Sponsor may request a teleconference to discuss the Division's feedback if they find it necessary. Depending on the impurities identified, the Sponsor and the Division may find it helpful to negotiate thresholds for their marketed drug product.

- The Sponsor asked the Division if the drug substance used for CHF 1538 would be adequate if it met the USP specifications for tobramycin. The Division informed the Sponsor that they would not likely be held to higher standards than comparable products. The Division added, however, that the ultimate determination would be made by the Chemistry, Manufacturing and Controls (CMC) review team.

- The Sponsor asked to discuss the response to clinical question 2; whether the studies conducted by the Sponsor would meet the definition of new clinical investigations. The Division indicated that the determination regarding whether studies are considered new clinical investigations can only be determined after the review is completed. The Division added that the studies seem to provide important safety information.

- The Sponsor informed the Division that CHF 1538 was technically a different formulation than TOBI (i.e., the components are not different, but the concentration of each component is different). The Agency acknowledged this.

- The Sponsor informed the Division that they (Sponsor) do not qualify for orphan drug status. The Division indicated that if Orphan status does not apply, the Sponsor will need to address pediatric requirements through either a deferral or waiver. The Sponsor and the Division discussed whether a waiver for children < 6 years of age would be appropriate. The Division indicated that the Sponsor may qualify for a waiver on the basis of the feasibility of conducting studies in this age group. The Sponsor stated they would likely submit a waiver request for pediatric patients < 6 years of age. The Division added that the pediatric drug development plan will need to be submitted with the NDA regardless.

- The Division informed the Sponsor that missing PK data would not have to be provided in SDTM format, but that it would be necessary to provide the information tabulated in the study report. The Division added that if information is not provided in a particular table, it should be available on the case report form (CRF).

- The Division informed the Sponsor that all demographic information should be provided in the study report in tabular format and that the Sponsor should focus on demographic information relevant to analyzing the Phase 1 data.

- The Division asked the Sponsor if they (Sponsor) collected any data beyond the primary endpoint. The Sponsor stated that no data was collected beyond the last study visit (i.e., 20 weeks).

- The Division asked what the expected timeline for NDA submission was. The Sponsor stated the target date for NDA submission is at the end of the 2nd quarter of 2010.

Minutes Prepared by: *{See appended electronic signature page}*
J. Christopher Davi, MS
Regulatory Project Manager

Concurrence by: *{See appended electronic signature page}*
Katherine A. Laessig, M.D.
Deputy Division Director

Dear Ms. Panico:

In response to the questions posed to the Agency in your briefing document dated June 18, 2009, (IND 72,068) we have the following preliminary responses in anticipation of our meeting on July 22, 2009:

1. In Module 1, there are several certifications required (e.g., debarment certification) that in a paper submission might usually be signed using a wet signature. For this eCTD submission, Chiesi proposes to omit the signature for these certifications in order to render them searchable, or alternatively, to provide scanned certifications as illustrated in the Attachment 2 of this meeting information package.

   Does the FDA agree with this approach?

   Agency Response: *No. You may not omit signatures for certifications. Please see the following website for a description of the types of signatures that are acceptable in electronic submissions:*

   http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/ucm113223.htm

2. Chiesi intends to submit a pilot eCTD submission in 4Q09. On 03 February 2009, Chiesi received an e-mail from FDA containing guidance on the content of a pilot submission. Regarding the recommended content (Attachment 3 of this meeting information package):

   a. Chiesi has not yet selected a vendor for the Structured Product Labeling (SPL). Therefore, Chiesi proposes to submit the sample content in 1.14.1.3 (Draft LabelingText) in MS Word format rather than SPL. Does the FDA agree with this approach?

   Agency Response: *Yes.*

   b. Chiesi's eCTD submission will not contain reports in 4.2.3.1 (Single Dose Toxicity) 4.3.2.1, or 5.3.5.2 (Study reports and related information of uncontrolled studies) since Chiesi will be filing a 505(b)(2) application, which will not contain this information. Chiesi proposes omitting these sections in the sample submission. Does the FDA agree?

   Agency Response: *Yes, it is acceptable to omit the section headings that will not contain information.*

3. Rather than using the electronic submissions gateway, Chiesi's sample eCTD submission will be sent to FDA on CD-Rom or DVD-R. Does the FDA agree with this approach?

   Agency Response: *Yes.*

4. Chiesi does not plan to submit a stability dataset (e.g, SAS or MS Excel files), although tability tables will be submitted in International Conference on Harmonization (ICH)-recommended format.

   Does FDA agree with this approach?

   Agency Response: *Yes*

5. In the meeting information package in Attachment 4, Chiesi has proposed a table of contents and filenames for the eCTD submission (proposed changes from FDA and ICH guidelines are presented in bold font). Does the FDA have any comments on the proposed filenames or the table of contents?

   Agency Response: *Please note that FDA does not use heading 5.3.7 for CRFs. Instead, CRFs and datasets should be located with the study they pertain to (see http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163175.pdf). Please refer to the Study Data Specification document for information on the Windows folder hierarchy for datasets:*

   http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163561.pdf

NONCLINICAL

1. In the pre-NDA meeting minutes dated 18 November 2005, FDA indicated the following:

   - "The Sponsor stated that they believed their nonclinical program (pending further detailed review by the FDA), in conjunction with information available to the FDA according to the 505(b)(2) process, would be adequate to provide the information necessary to support a 505(b)(2) NDA. The Division indicated that this was a reasonable assessment and did not anticipate that additional nonclinical studies would be needed. The Division recommended that the Sponsor request that the Division rely on its previous findings of safety from the Tobi NDA for support."

- "The Division stated that it is acceptable to correct the doses achieved in the inhalation studies with regard to respirable fraction. However, the Division noted that the Sponsor had not supplied a complete list of assumptions used to calculate the dose in the animal inhalation studies, and had only provided what was believed to be the respirable fraction. The Division stated that assumptions or measurements regarding deposition, respiration rate and body weight should be included. To calculate the inhaled dose of a substance, the Division recommended the use of the following equation:

  Inhaled Dose (mg/kg) = [Minute Volume (L/min) x Exposure Duration (min) x Aerosol Concentration (mg/L)] / Body Weight (kg)
  The Division stated that a pulmonary deposition factor of 10% for rats and 25% for dogs should be used."

Does the FDA still agree with these statements?

Agency Response: *Yes, these statements are still applicable.*

2. As described in the Chemistry, Manufacturing, and Controls (CMC) pre-NDA meeting information package (**SN 0013**), Chiesi plans to develop new chromatographic impurity methods for drug substance and drug product. Therefore, Chiesi has not yet completed impurities analyses for the NDA registration batches. In addition, several guidances have been released regarding impurities since the 2005 meeting. In light of the above information, please consider the following regarding impurities:

   a. Chiesi does not expect any observed impurity to exceed the levels for qualification stated in the ICH guidances Q3A and Q3B. However, if an impurity exceeds the ICH levels, and must be qualified, Chiesi believes that two *in vitro* genotoxicity studies (bacterial point mutation and chromosomal aberration studies) and one 28-day rat inhalation study would be adequate to qualify such an impurity. Does the FDA agree?

   b. Chiesi also does not expect any of the impurities that might be present to be subject to a structural alert. However, if an impurity appears to have a structural alert for genotoxicity, Chiesi would propose performing an Ames assay for bacterial mutation and an *in vivo* mouse micronucleus assay with systemic dosing. Chiesi believes the testing strategy described would be sufficient to qualify a genotoxic impurity. Does the FDA agree?

      Agency Response: *Regarding both 2 a and b, a bacterial mutagenicity test is not ideal for this product due to the cytotoxicity of tobramycin to Gram negative bacteria. We do agree that your basic strategy for qualifying impurities (genotoxic or not) appears appropriate.*

c. The Pulmonary Division requests a 10X safety factor in rat studies to qualify impurities. (That is, they test at 10X the planned specification limit for the impurity.) Chiesi believes that a 10X safety factor should also be acceptable to the Division of Anti-Infective and Ophthalmology Drug Products. Does the FDA agree?

Agency Response: *Yes, a 10X safety factor would be acceptable.*

3. Chiesi plans to (b) (4) (b) (4) adults. Juvenile animal studies, therefore, are not planned. Does the FDA agree?

Agency Response: *Yes, we agree that juvenile animal studies are not needed for this product.*

4. Chiesi plans to use the same language in their product label for reproductive and developmental toxicity, genotoxicity, and carcinogenicity as that currently used for Tobi. Is this acceptable to the FDA?

Agency Response: *Yes, we agree that this would be appropriate.*

CLINICAL MICROBIOLOGY:

1. Chiesi believes that the presentation of microbiological information in the eCTD, as described in section 6.2.2.1 of this meeting information package is appropriate. Does the FDA agree?

Agency Response: *This is acceptable to the FDA. However, to clarify, please note the following:*

- *Module 5, Clinical Study Reports, subsection 5.3.5.4, Other Study Reports. This section should contain the nonclinical study and clinical trial reports used in the construction of the summary information provided in subsection 2.7.2.4. All of the study and trial reports used to construct the summary report presented in section 2.7.2.4 should be cross-linked to the summary report. Both of these sections should be cross-referenced to each other.*

2. The facsimile from the FDA dated 19 June 2006 (**SN 0006**) indicated that "…it will be necessary to provide evidence that the susceptibility profiles of the infecting bacteria isolated from patients in foreign countries are similar to the susceptibility profiles of the infecting bacteria isolated from similar patients in the United States. One way that this can be accomplished is to provide MIC_{50s}, MIC_{90s}, and MIC ranges

for these bacteria isolated from CF patients in the foreign countries compared to the same information for bacterial isolates from CF patients in the United States. The MIC information should include information not only for tobramycin but for other antimicrobials that may be used to treat infections due to these bacteria in the cystic fibrosis population."

Chiesi will provide descriptive statistics of PA surveillance isolates (from the US) and clinical isolates (from foreign studies) treated with tobramycin and other antibiotics that could be used to treat infectious bacteria in CF patients. The intent is to compare the susceptibility profile of US and foreign isolates. Does the FDA agree with this approach?

Agency Response: *This is acceptable to the FDA.*

3. As stated above, Chiesi intends to provide descriptive statistics regarding its susceptibility data, but does not intend to provide the datasets associated with these statistics. Does FDA agree with this approach?

   Agency Response: *This is acceptable to the FDA.*

CLINICAL:

1. The following FDA positions were documented in the minutes from Chiesi's initial meeting with the FDA dated 18 November 2005:

   - "[The] clinical program in conjunction with information available to the division should provide the necessary information to support a 505(b)(2) NDA submission provided an appropriate nebulizer/compressor combination could be found for use in US patients."

   - "The initial and any subsequent tobramycin *in vitro* susceptibility test results for the patient isolates should be correlated with the clinical and microbiological outcome for each patient."

   Chiesi believes that none of these positions have changed. Does the FDA agree?

   Agency Response: *Yes, the statements above are consistent with our previous agreement and with the general rule for a 505(b)(2) NDA application.*

2. Chiesi believes that the clinical investigations (**CT01** and **CT02**), sponsored by Chiesi Farmaceutici SpA, meet the definition of "new clinical investigations" as described in 21 CFR 314.108 in that they are "essential to approval" of Chiesi's NDA. This NDA will, therefore, qualify for 3 years marketing exclusivity. Does the FDA agree?

   Agency Response: *This determination will be made by the Office of Generic Drugs post-approval.*

3. Given the relatively limited data involved, Chiesi plans to summarize the integrated study data in the text in eCTD Modules 2.7.3 and 2.7.4, and the integrated dataset, tables and appendices in Module 5 Section 5.3.5.3, as suggested in the Guidance for Industry, Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document, Example 4. Does the FDA Agree?

   Agency Response: *Yes, that approach appears reasonable.*

4. The Phase 1, crossover, single-dose, PK (**CP01**) study consisting of 11 randomized patients will be described fully in the NDA with regards to safety and efficacy findings, but will not be included in the integrated analyses of efficacy or safety as patients in this study were exposed to only single doses of both CHF 1538 and Tobi. Does the FDA agree with this approach for the integrated summary of efficacy (ISE) and integrated summary of safety (ISS)?

   Agency Response: *Yes, the Agency agrees with your proposed approach.*

5. Chiesi will perform patient subset analyses of efficacy and safety (for example, based on gender, and age and on baseline levels of forced expiratory volume in one second [FEV_1], minimal inhibitory concentration [MIC], and rhDNase use) using the combined **CT01** and **CT02** datasets. The key data analyzed will be the primary efficacy endpoint (for efficacy) and TEAEs and SAEs (for safety). If particular safety or efficacy concerns arise, the data will be further explored to evaluate the consistency of the findings within each trial. Does the FDA agree with this approach?

   Agency Response: *These analyses should be provided for individual studies, in addition to the combined analysis.*

6. Chiesi will perform drug:drug interaction analyses for efficacy (primary efficacy endpoint) and safety (treatment-emergent adverse events [TEAEs] and serious adverse events [SAEs]) using only the integrated Phase 2 (**CT01**) and Phase 3 (**CT02**) database, as this database provides the most power to detect meaningful interactions with repeated dosing of CHF 1538. Since CHF 1538 is an inhaled drug, the focus of this analysis will be on potential interactions with concomitant inhaled medications used in studies **CT01** and **CT02**. Drug:drug interactions of CHF 1538 in patients who received any concomitant antibiotic in these studies will also be explored. Does the FDA agree that this plan is acceptable?

Agency Response: *Yes.*

7. Chiesi has requested a waiver for pediatric studies of CHF 1538 in children less than 6 months of age. Does the FDA agree?

   Agency Response: *Yes, the condition in the indication (cystic fibrosis with Pseudomonas aeruginosa infection) does not exist in this age group.*

8. Chiesi plans to [redacted] (b) (4) (b) (4) (b) (4) Does the FDA agree?

   Agency Response: *Data are scant regarding the possible benefits of inhalational drug products for use in cystic fibrosis patients 6 months to 6 years of age. Besides, it is unclear whether you plan to seek an orphan status designation for your product. Evaluation for qualification for such status is the responsibility of the Office of Orphan Products Development (OOPD). Granting your product such a status would release you from the legal obligation to conduct any pediatric study(ies). It may be reasonable to request a waiver of pediatric studies in this age group, based on feasibility.*

We look forward to our discussion with you on July 22, 2009. If you have questions, Please contact me at (301) 796-0702.

J. Christopher Davi, MS
Senior Regulatory Project Manager

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
IND 72068	GI 1	CHIESI	CHF 1538
IND 72068	GI 1	CHIESI	CHF 1538

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/s/

KATHERINE A LAESSIG
08/20/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201820

ACKNOWLEDGE – CLASS 2 RESPONSE

Chiesi Pharmaceutical, Inc.
Attention: Erika Panico, RAC (US)
Vice President & Managing Director
9605 Medical Center Drive, Suite 380
Rockville, MD 20850

Dear Ms. Panico:

We acknowledge receipt on April 13, 2012, of your April 12, 2012, resubmission of your new drug application submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for CHF 1538 (tobramycin 300 mg/4 mL inhalation solution).

We consider this a complete, class 2 response to our August 25, 2011, action letter. Therefore, the user fee goal date is October 13, 2012.

If you have any questions, call Carmen DeBellas, Regulatory Project Manager, at (301) 796-1203.

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CARMEN L DEBELLAS
05/04/2012

From: DeBellas, Carmen
Sent: Thursday, January 26, 2012 7:32 AM
To: 'Erika Panico'
Subject: RE: NDA 201820: In vitro protocol feedback

Hi Erika,

All I can say is I am sorry it took so long to get back to you. This is the response from the Device reviewer

I have reviewed the slides and have determined that the proposed in vitro test plane is sufficient to address the remaining device-related questions. All information discussed will be required (see responses to Questions 5, 6, 8 and 11). The test methodology and pooling paradigm are appropriate from my point of view.

Carmen

Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

From: Erika Panico [mailto:epanico@chiesiusa.com]
Sent: Wednesday, January 11, 2012 2:34 PM
To: DeBellas, Carmen
Subject: NDA 201820: In vitro protocol feedback

Hi Carmen,

Happy New Year! I hope your holidays were good ones. I've been emailing eSub this week, asking them where we should place the compressor in vitro study protocols in the eCTD backbone. It turns out that they want us to submit it to the IND instead of the NDA. Are you okay with that? Our IND is paper-based.

Any news from Sugato De about whether the information we showed in our slides regarding the devices is enough?

Thanks,

Erika

Erika Panico, RAC (US)

Managing Director

Chiesi Pharmaceuticals Inc.

9605 Medical Center Drive, Suite 380

Rockville, MD 20850 USA

Phone: +1 301 424 2661 x782

Fax: +1 301 424 2924

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/s/

CARMEN L DEBELLAS
01/26/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201820

MEETING MINUTES

Chiesi Pharmacueticals, Inc.
Attention: Erika Panico, RAC
Vice President and Managing Director
9605 Medical Center Drive, Suite 380
Rockville, MD 20850

Dear Ms. Panico:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CHF 1538 (tobramycin 300 mg/4mL inhalation solution).

We also refer to the meeting between representatives of your firm and the FDA on December 16, 2011. The purpose of the meeting was to discuss proposals for the resubmission of NDA 201820.

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 Carmen DeBellas at (301) 796-1203.

Sincerely,

{See appended electronic signature page}

John J. Farley, MD
Acting Division Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type A
Meeting Category:	Complete Response Discussion
Meeting Date:	December 16, 2011
Application Number:	201820
Product Name:	CHF 1538 (tobramycin 300 mg/4mL inhalation solution)
Indication:	Management of cystic fibrosis patients with *Pseudomonas* aeruginosa
Sponsor/Applicant Name:	Chiesi Pharmaceuticals, Inc

FDA ATTENDEES

Dr. John Farley	Acting Division Director
Dr. John Alexander	Clinical Team Leader
Dr. Shrimant Mishra	Clinical Reviewer
Dr. Rapti Madurawe	Branch Chief, Office of New Drug Quality Analysis (ONDQA)
Dr. Dorota Matecka	Product Assessment Leader (ONDQA)
Dr. Shirkant Pagay	Chemistry Reviewer
Dr. Thamban Valappil	Biostatistics Team Leader
Ms. Caroline Fukuda	Project Manager
Dr. Carmen DeBellas	Project Manager
Mr. Sugato De	Biomedical Engineer, Center for Devices and Radiologic Health (telephone)

SPONSOR ATTENDEES	**Chiesi Pharmaceuticals**
Ms. Erika Panico	Vice President and Managing Director
Dr. Susan Gamble	Assistant Director, Regulatory Affairs
Dr. Helen Cicirello	Medical Director
Ms. Ching Lam	Manager of Pharmaceutical Technology
Dr. Mary Parry-Billings	Corporate Clinical Development Head
Dr. Annamaria Muraro	Data Management and Statistics Head
Mr. Paolo Patri	CMC Director
Ms. Tiziana Peveri	Strategic Product Enhancement Dept. Head
(b) (4)	CMC Consultant
	CMC Consultant
	CMC Statistics Consultant

1. BACKGROUND

The Sponsor submitted NDA 201820 on October 22, 2011. The Agency reviewed the NDA and on August 25, 2011 issued a Complete Response Letter. The Sponsor requested this meeting to

discuss recommendations made in the Agency's Complete Response Letter and to discuss future development.

2. DISCUSSION

The Sponsor received the Agency responses prior to the meeting. The meeting discussion consists of clarifications and questions of the Agency responses. The Sponsor provided a few slides which have been officially submitted to the NDA file.

Questions for Clarification (Questions 3, 4 and 5 discussed together):

3. Chiesi proposes to provide data on Total Drug Substance Delivered from one CF breathing pattern; data from Vios compressors (used in the to-be-marketed configuration) and TurboBOY (N and S) compressors (clinical configuration) will be presented in the re-submission of the NDA based on the experimental design described in Section 6.3 of this meeting package. Does the Agency agree that a single breathing pattern will be appropriate for this comparison?

Agency Response: The Agency agrees that a single breathing pattern will be appropriate to enable the comparison from a device perspective. The variances in drug effectiveness shown in the clinical study between pediatric and adult patients are likely to be a function of CF disease progression rather than differences in breathing pattern.

4. The presented single breathing pattern is based on observed patterns in CF patients (Browning, et. al. [5]). Does FDA agree with this choice of breathing pattern?

Agency Response: The breathing pattern presented is likely adequate for the purposes of comparing functional characteristics of the different compressors, especially given the variety of patients already studied in the clinical trials. However, we would note that data supporting this breathing pattern rests on testing in CF patients between the ages of 17-29 and with significant pulmonary dysfunction at baseline. Please comment on whether breathing patterns in younger, healthier CF patients might intrinsically differ to such a degree from the above breathing pattern such that more than one breathing pattern should be evaluated in the proposed in-vitro studies.

5. Does FDA agree with the proposed study design and sample size for the Total Drug Substance Delivered study?

Agency Response: We agree with your proposed study design and sample size for the evaluation of Total Drug Substance Delivered. Please note that this measurement will be compared to an assessment of total emitted mass (TEM) collected using the Next Generation Cascade Impactor.

Meeting Discussion:

After some discussion with Sponsor it was agreed that the Total Emitted Mass (TEM) and Total Drug Substance Delivered were two different entities and that results from these tests would not be equivalent. The Agency stated that trends for differences between the devices would be

comparable for the two analytical methods mentioned above. The Agency agreed that a single breathing pattern would be appropriate and that a second breathing pattern was not required.

QUESTION 6

6. In the Complete Response Letter, FDA requests the submission of a device module containing descriptive information about each device referenced in the NDA. Much of the information requested is proprietary to the device manufacturer and is not accessible to Chiesi. Chiesi has obtained letters from the manufacturer of the devices (PARI respiratory equipment) allowing Chiesi to cross-reference the 510(k) applications for the to-be-marketed device combination (PARI LC Plus nebulizer/PARI Vios compressor). Chiesi believes the information in the 510(k) applications along with the device information presented in this meeting package is sufficient to meet FDA's requests in Clinical/Delivery Devices Request 2 of the Complete Response Letter. Does FDA agree?

Agency Response: We appreciate the decision to allow for the cross-referencing of the individual 510(k) applications for the to-be-marketed device combination. However, this information does not enable a direct comparison of the technological differences between the proposed Vios Compressor and the Turbo Boy N and Turbo Boy S (the compressors used in the clinical study). Because the only change between the proposed device configuration and the configuration used in the clinical study is the compressor component, it is important to understand the specific differences between the compressors that may affect aerodynamic particle size distribution (APSD). Please provide a detailed comparison of the technological features and materials between the three aforementioned devices and describe any differences. At minimum, please provide the comparison of the following parameters: intended use, performance pressure/flow, materials (housing, cylinders and seals), filters, operating principles (piston pump, etc.), power supply, and target population. Please indicate whether any of the noted differences are expected to impact the APSD from the device.

Meeting Discussion:

The Agency informed Chiesi that the detailed information concerning the device is necessary in order to help the Agency better understand the device and explain any potential differences in the in vitro studies. If the in vitro data is equivalent between the to-be-marketed and clinical compressors, the detailed information is not required. The Agency stated that the reason for the request for detailed information was that the 510(k) applications had not been submitted recently, and the Agency was looking for the most up-to-date information. Chiesi provided information regarding the devices on their slides and asked whether the information provided was adequate. The Agency could not provide a response on the adequacy of the information provided during the meeting, but agreed to provide a response after the slides could be reviewed by CDRH. Samples of the three compressor devices (the PARI Vios®, PARI TurboBOY N and PARI TurboBOY S) and the PARI LC® Plus nebulizer were provided by the Sponsor at the meeting.

QUESTION 8

8. In this meeting package, Chiesi proposes statistical approaches to select the number of devices and analyze the in vitro results.

b. A population bioequivalence (PBE) evaluation (see Section 8.3.1.5) will be performed for selected key parameters of the NGI data from the Vios compressor (TEST) compared to the pooled TurboBOY N and TurboBOY S data (REFERENCE). Is the statistical approach (in vitro PBE) using pooled TurboBOY data as the REFERENCE acceptable to FDA?

Agency Response: From a device perspective, the appropriateness of pooling will be dependent on the types of differences between the TurboBoy N and TurboBOY S that may affect APSD specifications. The performance characteristics/APSD specifications of these devices are assumed to be similar to justify pooling. However, if they are different, pooling is not justified.

Meeting Discussion:

The Sponsor showed a slide titled, "Illustration of possible relations between Vios and TurboBOY data" (submitted officially after the meeting and attached to end of these minutes). After some discussion, the Agency stated that the Sponsor needed to provide data that would create two bridges.

1. Data to show comparability of drug delivery for the clinical trial and to-be-marketed device configurations for CHF1538

2. Data to show comparability of drug delivery between the to-be-marketed product and the approved reference product TOBI, which would establish a link to the previous findings of safety and efficacy necessary for a 505(b)(2) application.

The Agency commented on the five examples of results presented in the slide stating that examples 2, 3 and 4 might provide sufficient information to show comparability of the to-be-marketed and clinical trial device configurations but this would be a review issue. The Agency further commented that linking the TurboBOY N used in studies CT02 and CT03 is more important than the link to the TurboBOY S. Study CT02 is the important study, since it was placebo-controlled and was conducted over multiple dose cycles. The Agency pointed out that DeVilbiss Pulmo-Aide/TOBI arm of the in vitro study is important in case the TurboBOY N and/or TurboBOY S to Vios bridges cannot be created.

In addition, the Agency stated that since the safety profile of tobramycin has been established, slightly higher does delivered with the to-be-marketed device compared to doses delivered in the clinical trial device may be acceptable.

The discussion then turned to how data should be analyzed. The Agency stated that two 1-sided comparisons rather than pooling would be preferable but did not reject potential pooling of the TurboBOY N and TurboBOY S data if the data is similar.

The Sponsor clarified what items would be needed to compare to theVios/CHF 1538:

1. TurboBOY S - CHF 1538 - PARI LC Plus nebulizer
2. TurboBOY N - CHF 1538 - PARI LC Plus nebulizer
3. Pulmo-Aide - TOBI - PARI LC Plus nebulizer

and that the TurboBOY N-TOBI configuration may not be necessary for the comparison.

The Sponsor mentioned that the sample size of the three compressors would change if the two 1-sided comparison approach was used stating that the number of TurboBOY N and TurboBOY S compressors would increase and the number of Vios compressors would decrease, but that the number of all three compressors would be between 13 and 26.

The Agency stated that we are available to review study designs submitted.

QUESTION 11

11. In Clinical/Delivery Request 4 of the Complete Response Letter, FDA requests data demonstrating intra-and inter-sample variability; however, the requested information has already been provided to FDA through a combination of Chiesi's clinical studies and the 510(k) clearance process for the PARL LC Plus nebulizer and the PARI Vios compressor. Further, some of the requests are more appropriate to a different type of delivery system (e.g. a multi-dose reservoir dry powder inhaler on pMDI) than that used to deliver CHF 1538, which is delivered by a continuous flow nebulizer driven by a pneumatic pump. Therefore, Chiesi does not believe that this request is applicable to CHF 1538. Does the FDA agree?

Agency Response: FDA does not agree that an assessment of intra- and inter-sample variability is not applicable to the present submission for CHF 1538. These measurements are important to characterize repeatability of performance for a specific device sample, and variability between device samples from different batches. The proposed bridging study is expected to provide this type of assessment. FDA expects that device samples from different batches will be used to constitute 13 Pari LC Plus/Vios device configurations that will be used twice for a total of 26 runs. Similarly, there should be an assessment of repeatability based on the two runs for 13 separate devices. In addition, please note that the differences in APSD specifications due to inter- and intra-sample variability demonstrated for the to-be-marketed device configuration is expected to be comparable to the corresponding differences in APSD specifications between the to-be marketed configuration (Pari LC Plus/Vios Compressor) and the device configurations used in the clinical study. Please note that inter- and intra-sample variability is not exclusively linked to the type of delivery system. The consistency of the manufacturing process and user-error also contribute to these types of variability. Because the proposed device is a continuous flow nebulizer, FDA expects these types of variability to be minimal. Furthermore, due to the relative ease of use of the proposed device as compared to DPI and MDIs, user-error is not expected to contribute to the variability between samples.

Meeting Discussion:

The Agency clarified that the intra- and inter-sample variability for the Vios compressor only was necessary and that for the intra-sample variability assessment, the same compressor unit

should be used multiple times. Information for the inter-sample variability assessment should be provided by using different compressor lots with the same nebulizer unit.

QUESTION 1

1. Chiesi has reanalyzed and conducted sensitivity analysis on the primary endpoint and analogous secondary endpoints, i.e. FEV1 FVC and FEF25-75% (refer to Section 5.3 of this meeting package). The results of these re-analyses corroborate Chiesi's claim that CHF 1538 is significantly superior to placebo in terms of change from baseline in PFT after 3 "ON" cycles of treatment, and Chiesi believes that these re-analyses adequately address any concern regarding any impact that some inconsistent recording of/loss of data has on the pulmonary efficacy analysis for Study CT02. Does the FDA agree?

Agency response: In general, your method of recalculation of the various pulmonary function variables appears appropriate. However, full datasets and details of the recalculations need to be provided to the Division so that your findings can be corroborated and additional analyses can be performed. These datasets would include height and age datasets from the various sources, recalculated pulmonary function variables, etc. Also, please provide a document detailing what source data errors occurred at each site in CT02 (this can be clarified at the meeting if necessary); this will help the Division have a clearer understanding of the recalculations.

Meeting Discussion:

The Sponsor agreed to submit the clinical datasets and related define files for the re-analyses of the pulmonary function tests. The Agency stated that a revised CT02 Clinical Study Report was not necessary.

The Agency clarified what information on discrepancies is requested for NDA review.
The Agency is requesting that the following be provided:

1. Summary tables for each specific site with a listing of the type and number of discrepancies.
2. Patient listings indicating whether any discrepancies were identified and the type of discrepancies.
3. Only information for the PFT parameters at key visits (V2 and V8).
4. Providing a brief summary of the differences between the 4 analyses would be useful.

QUESTION 12

12. In the Complete Response Letter, FDA requests full audiometric results for trials CT01, CT02, and CT03 in order to have a better understanding of the changes in hearing threshold during the course of treatment. Chiesi considers ototoxicity to be a systemic toxicity of tobramycin. Pharmacokinetic profiles of CHF 1538 and TOBI indicate comparable systemic exposure and relative bioavailability, and the link between these two profiles was presented clearly in the NDA (reference Module 5.3.1.2, Study Report Body CP01). Additionally, Chiesi's proposed label warns of the potential risk of ototoxicity even though it was not evidenced in

clinical studies. The proposed label for CHF 1538 is therefore consistent with the label for TOBI and the class effect concerning the potential risk of ototoxicity known for aminoglycosides. Does the FDA agree that the comparable pharmacokinetic profiles of CHF 1538 and TOBI, as well as the use of the same ototoxicity language in Chiesi's proposed label and the approved label for TOBI, are sufficient to address the issue of ototoxicity, despite the absence of full audiometric results from CT01, CT02 and CT03?

Agency Response: We acknowledge your proposal to use similar language to what is currently in the TOBI label to describe any potential ototoxicity risk. However, it should also be noted that ototoxic risk from inhaled aminoglycosides is not clearly understood; reports of hearing loss have been reported in post-marketing for TOBI. Thus, full audiometric results would help to understand how hearing thresholds may or may not be affected by the study drug regardless of whether such changes in threshold met criteria for ototoxicity. However, we also realize that these studies were performed several years ago and primary source data may no longer be available. This issue can be discussed further at the meeting.

Meeting Discussion:
FDA confirmed that the audiometric data are not optimal for the analysis of changes over time; however, they accepted that the assessment of ototoxicity will be based on the previously-submitted data.

QUESTION 13
13. In the Complete Response Letter, FDA requested further clarifications for the CT03 laboratory shift tables provided in the original NDA. The requested tables and guide to interpretation are provided in this package. Does FDA agree that this information adequately addresses the request?

Agency Response: The information is adequate though not optimal; how to interpret variables such as LCS (Low Clinically Significant) and HCS (High Clinically Significant) remains unclear due to lack of any numerical reference. However, the mean and median tables submitted do provide additional information that is of benefit.

Meeting Discussion:

The Agency stated that it understood that lab results that fell outside the defined normal range were reviewed by the investigator who gave a qualitative judgment as to the clinical significance of the finding. The Sponsor stated that site specific normal values were provided in the original NDA submission.

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/s/

JOHN J FARLEY
02/03/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201820

INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Chiesi Pharmaceuticals, Inc.
Attention: Erika Panico, RAC (US)
Vice President and Managing Director
9605 Medical Center Drive, Suite 380
Rockville, MD 20850

Dear Applicant:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CHF 1538 (tobramycin 300 mg/4mL inhalation solution).

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by [redacted] (b) (4)[1] The pervasiveness and egregious nature of the violative practices by [redacted] (b) (4) has led FDA to have significant concerns that the bioanalytical data generated at [redacted] (b) (4) from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or "prep" run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or "prep" runs that prevented [redacted] (b) (4) and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by [redacted] (b) (4) during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

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

[1] These violations include studies conducted by [redacted] (b) (4).

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by [redacted] (b) (4) during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

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

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

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

If you have any questions regarding this letter, please contact Maureen Dillon-Parker, Chief, Project Management Staff, at (301) 796-0706. For any other issues regarding this NDA, please contact Carmen DeBellas, R.Ph., Pharm.D., Regulatory Project Manager, at (301) 796-1203.

Sincerely,

{See appended electronic signature page}

John Farley, MD, MPH
Acting Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

JOHN J FARLEY
10/03/2011

From: DeBellas, Carmen
Sent: Tuesday, August 09, 2011 9:11 AM
To: 'Susan Gamble'
Cc: 'Erika Panico'
Subject: RE: NDA 201820: Clarifications

Hi Susan,

We need two Clarifications:

1. Was the TurboBOY N compressor used only in the CT01/CT02 trials and whether both TurboBOY N and S compressors were used in the CT03 trials?

2.What is the difference between the two?

Thanks,
Carmen
Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

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/s/

CARMEN L DEBELLAS
08/09/2011

From: Gamalo, Mark
Sent: Tuesday, February 01, 2011 2:13 PM
To: DeBellas, Carmen
Subject: RE: Statistical Request

Thanks for all your help, Carmen! We have them for CT01 and CT02, but CT03 may take a day or so. I will let you know when we send them.

Kind regards,

Erika

Erika Panico, RAC (US)

Managing Director

Chiesi Pharmaceuticals Inc.

9605 Medical Center Drive, Suite 380

Rockville, MD 20850 USA

Phone: +1 301 424 2661 x782

Fax: +1 301 424 2924

Hi Carmen,

I only want the SAS codes for their primary efficacy results found in Section 11.4.1 of CSR for Study CT01, CT02, and CT03.

Thanks,
Mark

From: DeBellas, Carmen
Sent: Tuesday, February 01, 2011 2:10 PM
To: Gamalo, Mark
Subject: FW: Statistical Request

Hi Mark.

The Sponsor called and is a little unclear about the request. Do you want the SAS programs and for which studies? They don't have them for the PK studies.

Carmen

From: DeBellas, Carmen
Sent: Tuesday, February 01, 2011 11:37 AM
To: 'Erika Panico'
Subject: Statistical Request

Hi Erika,

Our statistical reviewer would like you to provide the SAS codes for your primary efficacy results.

Thanks,

Carmen

Carmen DeBellas, Pharm D. RPh.
Project Manager
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
301-796-1203

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/s/

CARMEN L DEBELLAS
02/02/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201820

FILING COMMUNICATION

Chiesi Pharmaceuticals, Inc.
Attention: Erika Panico, RAC
Vice President and Managing Director
9605 Medical Center Drive, Suite 380
Rockville, MD 20850

Dear Ms. Panico:

Please refer to your New Drug Application (NDA) dated October 22, 2010, received October 25, 2010, submitted under 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for CHF 1538 (tobramycin 300 mg/4mL inhalation solution).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is August 26, 2011.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by August 15, 2011.

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

Chemistry, Manufacturing and Controls:

1. There are significant changes between the clinically tested and to-be-marketed drug substance, drug product and the device combination. At this stage of review, it is unclear if the in vitro information provided is sufficient to bridge these multiple changes.

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

We do not expect a response to this letter, and we may not review any such response during the current review cycle.

We also request that you submit the following information:

Chemistry, Manufacturing and Controls:

1. Provide in a tabular format a side-by-side comparison of the Tobramycin for Inhalation Solution manufacturing process used by (b) (4) and Catalent, USA. The manufacturing process should also include the (b) (4). The comparison should include information on the process scale, process steps, in-process parameters and in-process tests (such as temperature control in preparation of tobramycin solution, pH, etc.). These processes should be of a minimum pilot scale.

2. Provide in a tabular format a side-by-side comparison of the (b) (4) the tobramycin solution) sourced from the two vendors in (b) (4) and the third vendor in (b) (4)). Provide a Letter of Authorization from each of the three (b) (4) vendors to access their respective DMF for the (b) (4).

3. The 12-month long-term stability update for the primary drug product batches should be provided by February 28, 2011.

4. Does the leachable study provided in the NDA include an evaluation of the label adhesive on the primary container? If not, provide information on leachables from the label adhesive.

5. Clarify if the osmolality values provided for the clinical and primary stability drug product batches (given in the Quality Overall Summary, Section 2.3.P-Table 3) are based on the USP test method.

Chemistry, Manufacturing and Controls (Microbiology Issues):

1. (b) (4)
2.

3. [redacted] (b) (4)

4. Please provide the microbiological product quality results of drug product hold time studies performed using the commercial processing equipment.

If you have not already done so, you must 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. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

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

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.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult the Division of Anti-Infective and Ophthalmology Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

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

We note that you have submitted pediatric studies with this application for pediatric patients 6 to 16. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this age group.

If you have any questions, call Carmen DeBellas, Regulatory Project Manager, at (301) 796-1203.

Sincerely,

{See appended electronic signature page}

Katherine A. Laessig, MD
Deputy Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

KATHERINE A LAESSIG
01/07/2011

Erika Panico

From: Erika Panico <epanico@chiesiusa.com>
Sent: Wednesday, December 01, 2010 2:02 PM
To: 'DeBellas, Carmen'
Subject: RE: CMC request changes
Signed By: epanico@chiesiusa.com

Hi Carmen,

One more thing – one of the requests is to provide comparative data for both the clinical and "to-be-marketed" device combinations using the "to-be-marketed" drug product (manufactured by Catalent [(b) (4)]). In the NDA, we have provided the comparative data, but the clinical device combination was tested with [(b) (4)] data. The only difference between the batches produced at [(b) (4)] and Catalent is the drug product manufacturing site; in fact, we have provided batch analysis results for both batches ([(b) (4)] in Module 3.2.P.5.4 and we believe there are no significant differences that would affect in vitro drug delivery results.

Knowing this, if FDA still wants Chiesi to provide results on the clinical device combination using Catalent [(b) (4)] drug product, we would be able to provide the data in 6 to 8 weeks from now given holiday schedules and the need to source the appropriate devices and drug product. The remainder of the response I can send out by EOB tomorrow. Please let me know the reviewers' thoughts on this.

Many thanks,

Erika

Erika Panico, RAC (US)
Managing Director
Chiesi Pharmaceuticals Inc.
9605 Medical Center Drive, Suite 380
Rockville, MD 20850 USA
Phone: +1 301 424 2661 x782
Fax: +1 301 424 2924

From: DeBellas, Carmen [mailto:Carmen.DeBellas@fda.hhs.gov]
Sent: Wednesday, December 01, 2010 12:47 PM
To: 'Erika Panico'
Subject: CMC request changes

Hi Erika,

I thought I should send this along since it may save you from doing some extra work.

CMC comment

Yes, that does change request #2. Comparative data for the [(b) (4)] combination is not necessary now.

We would still like to get the *in vitro* delivery data obtained with the clinical device combination using the "clinically tested [(b) (4)])" drug product. This data was probably generated for the EU application.

Hope this lightens the workload.

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/s/

CARMEN L DEBELLAS
12/02/2010

From: DeBellas, Carmen
Sent: Wednesday, December 01, 2010 12:47 PM
To: 'Erika Panico'
Subject: CMC request changes

Hi Erika,

I thought I should send this along since it may save you from doing some extra work.

CMC comment

Yes, that does change request #2. Comparative data for the (b) (4) compressor combination is not necessary now.

We would still like to get the *in vitro* delivery data obtained with the clinical device combination using the "clinically tested (b) (4)" drug product. This data was probably generated for the EU application.

Hope this lightens the workload.

Carmen

Carmen DeBellas, Pharm D. RPh.
Project Manager
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
301-796-1203

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/s/

CARMEN L DEBELLAS
12/02/2010

From: DeBellas, Carmen
Sent: Tuesday, November 30, 2010 2:46 PM
To: 'Erika Panico'
Subject: CMC Information request

Hi Erika,
I have a CMC information request

Please respond to the following information request within 2 business days.

1. What is the 510(k) application status for the LC Plus nebulizer, [redacted] (b) (4), Vios compressor, and [redacted] (b) (4) compressors? Provide the application # for the 510(k) approved devices.

2. You have provided comparative in vitro delivery data in the NDA for the clinical device combination and the [redacted] (b) (4) combination. However, the "to-be-marketed" device combination is the [redacted] (b) (4) nebulizer and [redacted] (b) (4) compressor. Provide comparative in vitro delivery data for the clinical and "to-be-marketed" nebulizer-compressor device combination using the "to-be-marketed (Catalent [redacted] (b) (4) " drug product. Additionally, provide the delivery data obtained for the clinical device combination using the "clinically tested [redacted] (b) (4) " drug product.

Carmen

Carmen DeBellas, Pharm D. RPh.
Project Manager
Division of Anti-Infective and Ophthalmology Products
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CARMEN L DEBELLAS
11/30/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201820

NDA ACKNOWLEDGMENT

Chiesi Pharmaceuticals, Inc.
Attention: Erica Panico
Vice President and Managing Director
9605 Medical Center Dive, Suite 380
Rockville, Maryland 20850

Dear Ms. Panico:

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: CHF 1538 (Tobramycin 300 mg/4 mL Inhalation Solution)

Date of Application: October 22, 2010

Date of Receipt: October 25, 2010

Our Reference Number: NDA 201820

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 24, 2010 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.

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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm

If you have any questions, call Kyong Hyon, Regulatory Project Manager, at (301) 796-0734.

Sincerely,

{See appended electronic signature page}

Frances V. LeSane
Chief, Project Management Staff
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CARMEN L DEBELLAS
11/03/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201820

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If you have any questions, call Carmen DeBellas, Regulatory Project Manager, at (301) 796-1203.

Sincerely,

{See appended electronic signature page}

Carmen DeBellas
Regulatory Project Management Staff
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CARMEN L DEBELLAS
11/02/2010