CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208294Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 208294 SUPPL # HFD #

Trade Name Bevespi Aerosphere

Generic Name Glycopyrrolate and Formoterol fumarate

Applicant Name Pearl Therapeutics

Approval Date, If Known 04/25/2016

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(2)

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

YES ☒ NO ☐

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

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

c) Did the applicant request exclusivity?

YES ☒ NO ☐

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

3 years

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☒

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

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

1. Single active ingredient product.

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

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES ☒ NO ☐

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

NDA# 207930 012827

NDA# 207923 020831

NDA# 022571 022007

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

summary for that investigation.

YES ☒ NO ☐

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

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

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

YES ☒ NO ☐

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

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

YES ☐ NO ☒

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

YES ☐ NO ☒

If yes, explain:

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

YES ☐ NO ☒

If yes, explain:

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

PT003006, PT003007, PT003008

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 # PT003006	YES ☐	NO ☒
Investigation # PT003007	YES ☐	NO ☒
Investigation # PT003008	YES ☐	NO ☒

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

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

Investigation # PT003006	YES ☐	NO ☒
Investigation # PT003007	YES ☐	NO ☒

Investigation # PT003008 YES ☐ NO ☒

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

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

PT003006, PT003007, PT003008

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 # PT003006 !
!
IND # 107739 YES ☒ ! NO ☐
! Explain:

Investigation # PT003007 !
!
IND #107739 YES ☒ ! NO ☐
! Explain:

Investigation # PT003008 !
!
IND #107739 YES ☒ ! NO ☐
! Explain:

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

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

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

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

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Brandi Wheeler
Title: Regulatory Project Manager
Date: 04/13/2016

Name of Office/Division Director signing form: Badrul A. Chowdhury
Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

BRANDI E WHEELER
04/25/2016

BADRUL A CHOWDHURY
04/25/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 208294 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Bevespi Aerosphere Established/Proper Name: Glycopyrrolate and Formoteral Dosage Form: MDI		Applicant: Pearl Therapeutics Agent for Applicant (if applicable):
RPM: Brandi Wheeler		Division: DPARP

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

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(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.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☒ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is April 25, 2016	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy 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: 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	☐ Yes ☒ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) 4/25/2016
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)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ 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 ☐ Patient Package Insert ☒ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ 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	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	Acceptable 09/15/2015 Review 09/08/2015
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☐ None 08/10/15 DMEPA: ☐ None 02/24/16 DMPP/PLT (DRISK): ☐ None 03/11/16 OPDP: ☐ None 03/09/16 SEALD: ☒ None CSS: ☒ None Product Quality ☐ None Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	08/10/2015 ☐ Not a (b)(2) 03/30/16
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

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

• This application is on the AIP
  ○ If yes, Center Director's Exception for Review memo *(indicate date)*
  ○ If yes, OC clearance for approval *(indicate date of clearance communication)*
	☐ Yes ☒ No
	☐ Not an AP action

❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 09/30/15 If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	04/20/2016, 04/13/2016,03/25/2016, 03/10/2016,03/02/2016, 03/01/2016 12/09/2015, 11/24/2015, 11/10/2015, 10/22/2015, 10/13/2015, 08/28/2015, 08/27/2015, 08/18/2015, 07/30/2015, 07/07/2015
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 06/02/2014
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 12/21/2012
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	

❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 04/25/2016
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 04/12/2016
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	08/25/2015, 03/21/2016
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ 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)*	Clinical Review page 16 03/21/2016
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(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)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested 03/23/2016
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None 08/25/2015, 03/15/2016

Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 08/04/2015, 03/14/2016
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☐ No separate review 03/28/2016
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 08/13/2015, 03/10/2016
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• Tertiary review (*indicate date for each review*)	☐ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☐ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☐ None 04/25/2016, 04/20/2016, 04/12/2016, 03/14/2016, 03/03/2016, 02/22/2016
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(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)*	04/25/2016
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ Facilities inspections (*action must be taken prior to the re-evaluation date*) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☒ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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/s/

BRANDI E WHEELER
04/25/2016

We refer to NDA 208294 for BEVESPI AEROSPHERE (glycopyrrolate and formoterol fumarate) inhalation aerosol and to your proposed revised labeling submission dated April 18, 2016. We are providing our labeling comments and recommendations in the attached marked up labeling. The proposed insertions are underlined and deletions are in strike-out. Please be advised that these labeling comments are not necessarily the Agency's final recommendations and that additional labeling comments may be forthcoming.

Submit revised labeling incorporating the changes shown in the attached marked up label via email (brandi.wheeler@fda.hhs.gov) to Brandi Wheeler by 4pm on April 21, 2016, followed by an official submission to the NDA. If there are any questions, contact Brandi Wheeler, Regulatory Project Manager, at 301-796-4495.

Drafted by: L Pei 04/20/16, M Wood 04/20/16,T Durmowicz 04/20/16
B Wheeler 04/20/16

Cleared by: L Jafari 04/20/16

Finalized by: B Wheeler 04/20/16

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

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/s/

BRANDI E WHEELER
04/20/2016

We refer to NDA 208294 for BEVESPI AEROSPHERE (glycopyrrolate and formoterol fumarate) inhalation aerosol and to your proposed revised labeling submission dated April 5, 2016. We are providing our labeling comments and recommendations in the attached marked up labeling. The proposed insertions are underlined and deletions are in strike-out. Please be advised that these labeling comments are not necessarily the Agency's final recommendations and that additional labeling comments may be forthcoming.

We have the following labeling comment noted below.

Prescribing Information

Section 11: Description

- Revise the chemical name of the glycopyrrolate drug substance to one of those in the USAN Dictionary.

Submit revised labeling incorporating the changes shown in the attached marked up label via email (brandi.wheeler@fda.hhs.gov) to Brandi Wheeler by April 18, 2016, followed by an official submission to the NDA. If there are any questions, contact Brandi Wheeler, Regulatory Project Manager, at 301-796-4495.

Drafted by: S Chin, T Durmowicz 04/13/16, C Bertha 04/13/16
B Wheeler 04/13/16

Cleared by: L Jafari 04/13/16

Finalized by: B Wheeler 04/13/16

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/s/

BRANDI E WHEELER
04/13/2016

Dear Dr. Fischer:

We refer to NDA 208294 for BEVESPI AEROSPHERE (glycopyrrolate and formoterol fumarate) inhalation aerosol and to your proposed revised labeling submission dated March 8, 2016. We are providing our labeling comments and recommendations in the attached marked up labeling. The proposed insertions are underlined and deletions are in strike-out. Please be advised that these labeling comments are not necessarily the Agency's final recommendations and that additional labeling comments may be forthcoming.

We also have the following labeling comments noted below.

Prescribing Information

(b) (4)

Instructions for Use and Medication Guide

- Changes reflect the Agency's efforts reduce redundancy, to make patient information more consistent and concise, and to include the information necessary for patients to safely take their medication. As part of these efforts, we have also implemented several formatting changes.

Carton and Container Labeling

- Include the full name of the DSPC excipient on the labels, i.e., 1,2-distearoyl-sn-glycero-3-phosphocholine.

- On revised label mock-ups, indicate the location of the lot number and the expiration date.

Submit revised labeling incorporating the changes shown in the attached marked up label via email (brandi.wheeler@fda.hhs.gov) to Brandi Wheeler by April 4, 2016, followed by an official submission to the NDA. If there are any questions, contact Brandi Wheeler, Regulatory Project Manager, at 301-796-4495.

NDA 208294
Glycopyrrolate/Formoterol fumarate
Pearl Therapeutics, Inc.

Drafted by: S Chin 03/23/16, T Durmowicz 03/23/16, C Bertha 03/23/16
B Wheeler 03/24/16

Cleared by: S Nabavian for L Jafari 03/25/16

Finalized by: B Wheeler 03/25/16

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

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/s/

BRANDI E WHEELER
03/25/2016

We are currently reviewing your submission dated March 8, 2016, which contained your revised label. We have the following comment:

(b) (4)

We are continuing to review your proposed label and will have additional edits which we will forward to you when completed. We will reschedule a labeling teleconference in the future if one becomes necessary.

If you have any questions, please contact Brandi Wheeler, Regulatory Project Manager, at 301-796-4495.

NDA 208294

Drafted by: T Durmowicz 03/10/16
B Wheeler 03/10/16

Cleared by: L Jafari 03/10/16

Finalized by: B Wheeler 03/10/16

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/s/

BRANDI E WHEELER
03/10/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208294

INFORMATION REQUEST

Pearl Therapeutics, Inc.
Attention: Liuda Shtohryn, Pharm.D.
Senior Director, CMC Regulatory Affair
4222 Emperor Boulevard, Suite 560
Durham, NC 27703

Dear Dr. Shtohryn:

Please refer to your New Drug Application (NDA) dated and received June 25, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bevespi Aerosphere (glycopyrrolate and formoterol fumarate) Inhalation Aerosol.

We are reviewing the Chemistry Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA by March 9, 2016.

1. Your proposed combination product must comply with 21 CFR Part 4 regulations which describe how manufacturers are to meet the applicable CGMP requirements based on the constituent parts of the combination product. Please confirm the CGMP operating system you plan to use to manufacture the finished combination product.

2. If you do plan to operate under a streamlined approach [as provided in 21 CFR Part 4.4(b)] such that you will manufacture according to the drug CGMPs (21 CFR 210/211), you must also comply with applicable Quality System regulations (21 CFR 820) as outlined in 21 CFR Part 4.4(b)(1). In your response, please provide the following for review:

   a) A summary of the firm's management structure with executive responsibility who manage, perform, and assess work affecting quality of the product and related controls to ensure that the firm's quality policies are appropriately implemented and followed, and the product appropriately designed and manufactured in conformance with CGMP requirements, including quality system requirements met as per 21 CFR 820.20.

   b) A summary of the firm's design control system under 21 CFR 820.30 must be included for the device constituent part and combination product. The design control information

should include initial design, planning and development, design input, design output, design review, design transfer, design verification, and design validation that meets the proposed intended use of the final combination product, design changes, and design history file. For changes made to the device constituent part of the combination product, the impact of the design changes on the overall combination product performance should be considered and documented. All the design control activities must be documented in the Design History File (DHF) and subjected for design reviews.
In addition, the location of DHF should be provided to the Agency for the facility inspection determination.

c) Summary of information pertaining to the Purchasing Control as per 21 CFR 820.50 to demonstrate controls and documentation for components, products, or services(example sterilization) received at the sponsor's facility for use in the manufacture of the combination product. The summary should include the applicant's evaluation process of their suppliers that meet the manufacturing acceptance criteria of the combination product specifications. Notification of changes by the suppliers should be considered in the firm's Purchasing/Supplier agreement as changes to incoming specification can impact the safety and effectiveness of the final combination product.

d) Summary of information related to Corrective and Preventive Actions (CAPA) as per the requirement of 21 CFR 820.100. CAPA procedures are used to determine the cause of problems and non-conformances, and the appropriate measures used to correct and prevent such problems and non-conformances from recurring. The CAPA system must account for investigations into failures in the device constituent. CAPA activities for the analysis of sources of quality data to identify existing and potential cause of nonconformance, related investigations, and actions considered to correct and prevent recurrences of problems and non-conformances, including the verification or validation of the actions should be documented under the firm's CAPA System as described in 21 CFR 820.100.

Please note that combination products manufactured under the CGMP drug operating system, the Applicant/Licensure must also fulfill the requirements under 21 CFR Part 4.4b to show compliance to 21 CFR Part 4 for the finished combination product. To assist in the preparation of the above summaries related to the 21 CFR 820.20, 21 CFR 820.30, 21 CFR 820.50 And 21 CFR 820.100, we recommend the FDA Guidance 'Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,' (2003): http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.

If you have any questions, please contact me at (240) 402-2691.

Sincerely,

Bamidele F. Aisida -A

Digitally signed by Bamidele F. Aisida -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001703308, cn=Bamidele F. Aisida -A
Date: 2016.03.02 12:37:27 -05'00'

Florence Aisida, Pharm. D., B.C.P.S
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

We refer to NDA 208294 for BEVESPI AEROSPHERE™ (glycopyrrolate and formoterol fumarate) inhalation aerosol and to your proposed labeling submitted on June 25, 2015.

After initial review, we have the following comments regarding your proposed label to provide the rationale for our revisions and requested changes. We are also providing our labeling comments and recommendations in the attached marked up labeling. The proposed insertions are underlined and deletions are in strike-out. While the outline provided is for the body of the package insert, corresponding changes should also be carried to the Highlights section and Table of Contents. Note that these comments are not all-inclusive, and we may have additional changes to the label which may be forthcoming.

General Comments

- We have made revisions throughout your proposed label to establish consistency across similar product labels and where relevant, to match language used in reference product labels.
- We changed references to the doses used in clinical trials to the total dose delivered via 2 inhalations (i.e., glypyrrolate 18 mcg and formoterol fumarate 9.6 mcg).
- In other areas of the label or carton and container that do not refer directly to clinical trials, revise the presentation of the strength and dosage form so that it is easily recognized:

  Bevespi Aerosphere
  (Glycopyrrolate and Formoterol Fumarate) Inhalation Aerosol
  9 mcg/4.8 mcg per inhalation

- Ensure that the modifier “Aerosphere” has equal prominence to the root name “Bevespi”.

Section 2: Dosage and Administration

- Consider adding a paragraph about the dose indicator, i.e,, that BEVESPI AEROSPHERE includes a dose indicator attached to the canister, some information of how the indicator works, and instructions to discard when the indicator shows that there are zero doses remaining. Similar instructions may be added to Section 17 as well.

(b) (4)

Section 3: Dosage Forms and Strengths

- Per 21 CFR 201.57(c)(4), this section must contain information about the dosage form (inhalation aerosol).
- Consider stating that the canister has an attached dose indicator.

Section 7: Drug Interactions

- We made revisions throughout the section to be consistent with other similar product labels.
- Study results are not typically included in this section of the label; therefore, we revised the language (b) (4) regarding beta blocker use.

Section 8: Use in Specific Populations

(b) (4)

Section 11: Description

- Per 21 CFR 201.57 (c)(12), this section must contain the Proprietary and established names of the product, the pharmacologic class, the dosage form, and the route of administration.

Section 12.3: Pharmacokinetics

(b) (4)

Section 13: Nonclinical Toxicology

- Redundant sections were removed.

(b) (4)

Section 14.2: Dose-Ranging Trials

- In general, the dose-ranging section has been streamlined. Since neither component is a new molecular entity and both drugs are well-known, it is not necessary to include every dose-ranging study conducted.

- (b) (4) dose selection was primarily based upon dose-ranging of the individual components, (b) (4).

Section 14.3: Confirmatory Trials

- The results provided in Table 2 are change from baseline in trough FEV1 (b) (4) at week 24, and should be described as such. We recommend reformatting the table to improve readability and ease interpretation. For an example, refer to a similar table in the glycopyrrolate/indacaterol (Utibron) label.

(b) (4)

- In (b) (4) change the GP and FF doses in the legends to 18 mcg and 9.6 mcg, respectively.

- The SGRQ response rate was added because it was included in the glycopyrrolate/indacaterol label.

Carton Labeling

- Relocate 'Shake inhaler well before using' from the side panel to the principal display panel to mitigate the risk that this important information this overlooked. To allow space for this statement, we recommend you consider decreasing the size of the graphics.

- The drug barcode is often used as an additional verification before drug administration in the inpatient setting; therefore, it is an important safety feature that should be part of the label whenever possible. We request you add the product barcode to each individual carton as required per 21CFR 201.25(c)(2).

- Remove the statement '(b) (4)

- For consistency with the full Prescribing Information, revise the 'Discard the inhaler…' statement under 'Date foil pouch opened:' to read: Discard the inhaler when the labeled number of inhalations have been used or within 3 months of opening the foil pouch, whichever comes first.'

Canister Label

- Add the lot and expiration date to the canister label.

Carton Labeling and Overwrap Foil

- Revise the usual dosage statement to read: ‘2 inhalations twice daily’.

Submit revised labeling incorporating the changes shown in the attached marked up label via email (brandi.wheeler@fda.hhs.gov) to Brandi Wheeler by March 8, 2016
The email should be followed by an official submission to the NDA.

Drafted by: S Chin 02/29/16, T Durmowicz 02/29/16, L Pei 02/26/16, M Wood 02/26/16, C Bertha 02/26/16, S Agarwal 02/26/16, Y Ren 02/26/16, B Abugov 02/26/16, F Cooner 02/26/16

Cleared by: L Jafari 02/29/16

Finalized by: B Wheeler 03/01/16

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

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/s/

BRANDI E WHEELER
03/01/2016

Your NDA 208294 submitted on June 25, 2015 is currently under review. We have the following request for information.

1. For studies PT003006 and PT003007, provide the programs and any additional datasets needed to generate table 2.4.3.1 for SGRQ response rates.

Provide a response to the request by email (Brandi.Wheeler@fda.hhs.gov) or facsimile (301-796-9728), by Wednesday, December 23, 2015. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Brandi Wheeler, Regulatory Project Manager, at 301-796-4495.

NDA 208294

Drafted by: B Abugov 12/9/15 / F Cooner 12/9/15
B Wheeler 12/9/15

Cleared by: L Jafari 12/9/15

Finalized by: B Wheeler 12/9/15

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/s/

BRANDI E WHEELER
12/09/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208294

INFORMATION REQUEST

Pearl Therapeutics, Inc.
Attention: Liuda Shtohryn, CMC Regulatory Affairs
4222 Emperor Boulevard, Suite 560
Durham, NC 27703

Dear Dr. Shtohryn:

Please refer to your New Drug Application (NDA) dated and received June 25, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bevespi Aerosphere (glycopyrrolate and formoterol fumarate) Inhalation Aerosol.

We are reviewing the Chemistry Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA by December 8, 2015.

1. *Provide commercial master batch production record for the manufacture of GFF-MDI.*
2. *Provide updated stability data as soon as it becomes available.*
3. *Your application referenced Drug Master File (DMF III) (b) (4) and Drug Master File (DMF IV) (b) (4), both were found inadequate to support your submission. A deficiency letter was sent to the DMF holders on November 18, 2015.*

If you have any questions, please contact me at (240) 402-2691.

Sincerely,

Bamidele F. Aisida -A

Digitally signed by Bamidele F. Aisida -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001703308, cn=Bamidele F. Aisida -A
Date: 2015.11.24 09:40:06 -05'00'

Florence Aisida, Pharm. D., B.C.P.S
Regulatory Business Project Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

From: Aisida, Bamidele (Florence)
To: "Tracy Fischer"
Subject: IR request NDA 208294
Date: Tuesday, November 10, 2015 10:18:00 AM

Dear Dr. Fischer,

We are reviewing the Chemistry Manufacturing, and Controls sections of your submission and have the following information request. We request a written response in order to continue our evaluation of your NDA by November 24, 2015.

1. Provide the following information for the Formoterol Fumarate Inhalation Aerosol; PT005 and Glycopyrronium Inhalation Aerosol; PT001 used in studies PT003006 and PT003007
    a. Formulation
    b. Specification, including test method for measurement of the APSD. Reference may be made to the test method in the NDA used for the combination product, if applicable.
    c. Batch analysis

2. Provide the details of the operation of the Next Generation Impactor and the plate numbers used to calculate the Fine Particle Mass for the combination product in the NDA .

Thanks,

Florence Aisida, Pharm.D,BCPS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (240) 402-2691
Email: bamidele.aisida@fda.hhs.gov

Your NDA 208294 submitted on June 25, 2015, is currently under review. We have the following request for information:

1. Submit an ADSL dataset for pooled trials 3006 and 3007 with the ITTFL variable included.

2. Provide an ADAE analysis dataset with pooled data from trials PT003006, PT003007, and PT003008. Include the APHASE variable to indicate if the AE occurred during the lead-in or extension study.

3. Provide medical/surgical history and cardiovascular risk factor tables (ISS Phase 3, Tables 1-16 and 1-17) with only unique subjects. The current tables appear to count patients who enrolled under multiple subject ID numbers as separate patients.

4. For tables of demographics and baseline characteristics in the pooled ITT population (ISE Phase 3, Tables 3-6, 3-8, 3-10, 3-12), clarify which unique subject ID was used to provide the data for the six subjects which were included in the ITT population more than once.

5. Using 52-week data from the integrated phase 3 pivotal and long-term studies (PT003006, PT003007, and PT003008), submit the following tables from the PT003008 clinical study report (7-3, 7-4, 7-10, 7-25, 7-26, 7-29, 7-30, 7-31, 7-33, and 7-38) to include a column for the 26-week placebo treatment group.

Submit the requested information via email to Brandi.Wheeler@fda.hhs.gov or facsimile to 301-796-9728, by close of business, Monday, November 2, 2015, followed by an official submission to the NDA. If you have any questions, please contact Brandi Wheeler, Regulatory Project Manager, at 301-796-4495.

NDA 208294

Drafted by: S Chin / T Durmowicz 10/21/15
B Wheeler 10/21/2015

Cleared by: SNabavian (for LJafari)/10.21.2015

Finalized by: B Wheeler 10/21/15

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/s/

BRANDI E WHEELER
10/22/2015

PeRC Meeting Minutes
September 30, 2015

PeRC Members Attending:
Hari Cheryl Sachs
Linda Lewis
Gettie Audain
Lily Mulugeta
Thomas Smith
Shrikant Pagay NON-RESPONSIVE
Barbara Buch
Daiva Shetty
Wiley Chambers
Meshaun Payne
George Greeley
Freda Cooner
Gregory Reaman
Michelle Roth-Cline
Peter Starke NON-RESPONSIVE
Adrienne Hornatko-Munoz NON-RESPONSIVE
Ikram Elayan
Shrikant Pagay

Agenda

NON-RESPONSIVE

	NDA 208294	Glycopyrrolate/Formoterol MDI (Full Waiver with Agreed iPSP)	DPARP	Brandi Wheeler	COPD

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NON-RESPONSIVE

Glycopyrrolate/Formoterol MDI (Full Waiver with Agreed iPSP)

- Proposed Indication: COPD
- *PeRC Recommendations:*
  - The PeRC concurred with the sponsor's plan for a full waiver because the condition does not occur in pediatric patients and studies are not feasible as stated in their Agreed iPSP.

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/s/

MESHAUN L PAYNE
10/16/2015

From: Aisida, Bamidele (Florence)
To: "tfischer@pearltherapeutics.com"
Subject: NDA 208294 CMC Information Request
Date: Tuesday, October 13, 2015 12:16:03 PM

Dear Dr. Fischer,

We are reviewing the Chemistry Manufacturing, and Controls sections of your submission and have the following information request. We request a written response in order to continue our evaluation of your NDA by October 27, 2015.

Explain why there is no test for retention times of the glycopyrronium and formoterol fumarate in the System Suitability Test for Method ATM-0016.

Thanks,

Florence Aisida, Pharm.D,BCPS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (240) 402-2691
Email: bamidele.aisida@fda.hhs.gov

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208294

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Pearl Therapeutics, Inc.
4222 Emperor Boulevard, Suite 560
Durham, NC 27703

ATTENTION: Tracy Fischer, Pharm. D.
Senior Director, Regulatory Affairs

Dear Dr. Fischer:

Please refer to your New Drug Application (NDA) dated and received June 25, 2015 submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Glycopyrrolate and Formoterol Fumarate Inhalation Aerosol, 9 mcg/4.8 mcg per actuation.

We also refer to your correspondence dated and received July 10, 2015, requesting review of your proposed proprietary name, Bevespi Aerosphere.

We have completed our review of the proposed proprietary name, Bevespi Aerosphere and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your July 10, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

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

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nichelle Rashid, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application, contact Brandi Wheeler, Regulatory Project Manager in the Office of New Drugs, at (301) 796-4495.

Sincerely,

{See appended electronic signature page}

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

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/s/

TODD D BRIDGES
09/15/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208294

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

Pearl Therapeutics, Inc.
4222 Emperor Boulevard Suite 560
Durham, NC 27703

Attention: Tracy Fischer, PharmD
Senior Director, Regulatory Affairs

Dear Dr. Fischer:

Please refer to your New Drug Application (NDA) dated June 25, 2015, received June 25, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for glycopyrrolate and formoterol fumarate 9/4.8mcg inhalation aerosol.

We also refer to your amendments dated July 8, 29, and 30, and August 7, and 21, 2015.

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 April 25, 2016.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by March 28, 2016.

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

Clinical
We note that the size of your safety database is substantially smaller than for other products indicated for the treatment of COPD. The adequacy of your safety database will be a review issue.

We are providing the above comments to give you preliminary notice of potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

Chemistry, Manufacturing, and Controls

1. Regarding the drug substance:

    a. Nomenclature and structural information for glycopyrronium bromide and formoterol fumarate (under 3.2.S.1.1 and 3.2.S.1.2).

    b. A listing of all drug substance manufacturing facilities (under 3.2.S.2.1). Include FEI and/or DUNS numbers and clearly describe the manufacturing responsibilities that are carried out at each facility.

    c. A table summarizing the identity and source of any impurities comprised by the drug substance (under 3.2.S.3.2).

    d. The complete set of drug substance release specifications for glycopyrronium bromide and formoterol fumarate. Indicate those release tests that are repeated by the drug product manufacturer as part of the confirmatory testing of drug product components that is required under 21 CFR §211.84(d).

2. Regarding the drug product

    a. A description of the test methods used to identify the extractables.

    b. Data demonstrating the chemical stability of the 1,2-distearoyl-*sn*-glycero-3-phosphocholine, including under accelerated conditions.

PRESCRIBING INFORMATION

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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

1. All headings in Highlights must be presented in the center of a horizontal line. Extend each horizontal line over the entire width of the column.

2. In the Table of contents, all subsection headings must be indented and not bolded. Subsection headings should not be bolded. Remove additional periods after subsection 13.1.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by **September 25, 2015**. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

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

Please respond only to the above requests for information by **September 25, 2015**. 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.

We acknowledge your request for a waiver of the requirement that the Highlights of Prescribing Information be limited to no more than one-half page. We will consider your request during labeling discussions.

PROMOTIONAL MATERIAL

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

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

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

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Brandi Wheeler, Regulatory Project Manager, at (301) 796-4495.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, MD, PhD
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

BADRUL A CHOWDHURY
08/28/2015

Your NDA 208294 submitted on June 25, 2015 is currently under review. We have the following request for information:

1. For clinical trials Study Protocols PT003006 and PT003007, respectively, submit updated contact information for the study site principal investigator (i.e., physical street address, phone, fax, email).

2. Submit the study subject data listing information request below as pdf files, organized per clinical study investigator site separately. Provide the following the study subject data listings that should capture the following, as applicable for the following principal investigators: Enrique Cifuentes, MD (PT003006 Site 6078; PT003007 Site 7447m and PT003008 Site 6078), V. Jerome Mirkil, MD (PT003006 Site 6079, PT003007 Site 7450, PT003008 Site 6079) and Robert Garver, Jr., MD (PT003006 Site 6021).

   a. Subject discontinuations (If applicable application per treatment group: site subject number, screening visit date, randomization date (if applicable), date of first dose/last dose, date of discontinuation, reason for discontinuation).

   b. Subject assignment per treatment arm (randomization group, as applicable).

   c. Concomitant medication list (non-study medications).

   d. All adverse events (If applicable pretreatment group: preferred term/investigator entry, date start/stopped, severity/resolution, serious adverse event (SAE [yes/no], death [yes/no]).

   e. Primary study efficacy endpoint.

   f. Secondary endpoints.

   g. Any protocol deviation/s or violation/s.

Please provide a response to the requests by email (Brandi.Wheeler@fda.hhs.gov) or facsimile (301-796-9728), by Monday, August 31, 2015. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please, contact Brandi Wheeler, Regulatory Project Manager, at 301-796-4495.

NDA 208294

Drafted by: A Orencia 08/27/2015
B Wheeler 08/27/2015

Cleared by: NTon for LJafari 08/27/2015

Finalized by: B Wheeler 8/27/2015

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/s/

BRANDI E WHEELER
08/27/2015

We have the following clarification regarding our information request dated July 30, 2015. We are also providing responses to your reply which was submitted on August 7, 2015. We acknowledge and agree with your request to provide all information by mid-September.

1. We would like to provide a clarification regarding our July 30, 2015, request for tipping point analyses. In particular, results from tipping point analyses depend not only on the difference for missing data between placebo and treatment, but may also depend on the specific values of placebo and treatment for which the difference was calculated.

   Provide results from your tipping point analyses on a two dimensional grid, with deviations from observed adjusted means on the x- and y- axes. For example, a possible template for tipping point analyses regarding change from baseline SGRQ would provide lsmean effects as in Table 1 and associated p-values in Table 2. Values at [0, 0] in Table 1 would indicate results where the adjusted mean of imputed values for each treatment arm corresponds to that obtained from observed data.

Table 1. Reduction from Baseline SGRQ, Adjusted Mean Differences between Treatment **xx** and Placebo

Placebo Change from Baseline for Missing Data	*Treatment **xx** Change from Baseline for Missing Data*								
	-16	-12	-8	-4	0	4	8	12	16
-16									
-12									
-8									
-4									
0									
4									
8									
12									
16									

Table 2. Reduction from Baseline SGRQ, P-Values for Differences Between Treatment **xx** and Placebo

Placebo Change from Baseline for Missing Data	*Treatment **xx** Change from Baseline for Missing Data*								
	-16	-12	-8	-4	0	4	8	12	16
-16									
-12									
-8									
-4									
0									
4									
8									
12									
16									

2. In your response to our information request sent on July 30, 2015, you asked the following questions.

   Does this satisfy the Agency's request to provide analyses that use observed data, without any imputation?

   FDA Response: This request was merely a starting point for the tipping point analyses, not a request for additional analyses using observed data.

   Does the Agency agree that it is not necessary to conduct a tipping point sensitivity analysis for peak FEV_1 on Day 1?

   FDA Response: Yes we agree. As there were only three subjects with missing data across the two studies, tipping point analyses is not required.

   Does the Agency agree that it is not necessary to conduct a tipping point sensitivity analysis for the SGRQ responder analysis at Week 24?

   FDA Response: No, we do not agree. Conduct tipping point analyses for SQRQ response rate at Week 24. These analyses should vary the response rate in subjects with missing data among the subset of subjects in the active and placebo arms. The case of where all subjects with missing data are considered non-responders is a subset of these tipping point analyses. You must also consider the possibility that subjects with missing data in the active arm had worse outcomes (fewer responders) than subjects in the placebo arm. For more information, see item 1 above.

Please provide a response to the requests by email (Brandi.Wheeler@fda.hhs.gov) or facsimile (301-796-9728), by Tuesday, September 15, 2015. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please, contact Brandi Wheeler, Regulatory Project Manager, at 301-796-4495.

NDA 208294

Drafted by: B Abugov/ D Petullo 08/18/2015
B Wheeler 08/18/2015

Cleared by: L Jafari 08/18/2015

Finalized by: B Wheeler 08/18/2015

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/s/

BRANDI E WHEELER
08/18/2015

Your NDA 208294 submitted on June 25, 2015 is currently under review. We have the following request for information:

1. Provide the programs and datasets used in Study PT003007 (Table 2.4.3.1) to analyze SGRQ response rate in the ITT population.

2. For studies PT003006 and PT003007, repeat your ITT analyses for change from baseline trough FEV1 at Week 24, change from baseline trough FEV1 over 24 weeks, peak change from baseline FEV1 within 2 hours post-dose at Day 1, mean change from baseline SGRQ at Week 24, SGRQ response rate at Week 24, and change from baseline in use of rescue medication over 24 weeks using only observed data, without any imputation.

Provide tipping point sensitivity analyses for these endpoints to examine the potential effect of missing data on the results. The tipping point analyses should employ the same models as your primary analyses, with multiple imputations varying assumptions about average values among the subsets of patients who were missing data. The goal of these tipping point analyses is to identify assumptions about the missing data under which the conclusions change, i.e., under which there is no longer evidence of a treatment effect. Then, the plausibility of those assumptions can be discussed.

Provide the datasets and programs for these analyses. The analysis datasets should include columns which clearly indicate whether each observation and the associated baseline measurement was missing, observed while the patient was on randomized treatment, or observed after the patient discontinued randomized treatment

Please provide a response to the requests by email (Brandi.Wheeler@fda hhs.gov) or facsimile (301-796-9728), by Thursday, August 20, 2015. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please, contact Brandi Wheeler, Regulatory Project Manager, at 301-796-4495.

NDA 208294

Drafted by: B Abugov/ D Petullo 07/29/2015
B Wheeler 07/29/2015

Cleared by: L Jafari 07/30/2015

Finalized by: B Wheeler 07/30/2015

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/s/

BRANDI E WHEELER
07/30/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208294

NDA ACKNOWLEDGMENT

Pearl Therapeutics, Inc.
4222 Emperor Boulevard Suite 560
Durham, NC 27703

Attention: Tracy Fischer, PharmD
Senior Director, Regulatory Affairs

Dear Dr. Fischer:

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: Glycopyrrolate and formoterol fumarate 9/4.8mcg inhalation aerosol

Date of Application: June 25, 2015

Date of Receipt: June 25, 2015

Our Reference Number: NDA 208294

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 August 24, 2015, in accordance with 21 CFR 314.101(a).

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

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

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory

registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at http://www.fda.gov/opacom/morechoices/fdaforms/default.html.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at: http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm. Additional information regarding Title VIII of FDAAA is available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html. Additional information for registering your clinical trials is available at the Protocol Registration System website http://prsinfo.clinicaltrials.gov/.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 208294** submitted on June 25, 2015, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

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 Pulmonary, Allergy, and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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

If you have any questions, call me, at (301) 796-4495.

Sincerely,

{See appended electronic signature page}

Brandi Wheeler, PharmD
Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

BRANDI E WHEELER
07/07/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 107739

MEETING MINUTES

Pearl Therapeutics, Inc.
200 Saginaw Dr.
Redwood City, C A 94063

Attention: Tracy Fischer, Pharm.D.
Senior Director, Regulatory Affairs

Dear Dr. Fischer:

Please refer to your Investigational New Drug Applications (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for glycopyrrolate and formoterol fumarate (GFF) inhalation aerosol, being developed for maintenance treatment (b) (4) with chronic obstructive pulmonary disease (COPD).

We also refer to the meeting between representatives of your firm and the FDA on June 2, 2014. The purpose of the meeting was to discuss clinical/statistical and regulatory plans for the GFF NDA submission.

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 me at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Christine Chung, R.Ph.
CDR, U.S. Public Health Service
Program Coordinator
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: June 2, 2014
Meeting Location: White Oak Building 22, Conference Room: 1419

Application Number: IND 107739
Product Name: Glycopyrrolate and formoterol fumarate (GFF) inhalation aerosol
Indication: Chronic obstructive pulmonary disease (COPD)
Sponsor/Applicant Name: Pearl Therapeutics, Inc. (Pearl)

Meeting Chair: Badrul Chowdhury, Director
Meeting Recorder: Christine Chung, Regulatory Project Manager

FDA ATTENDEES:

Badrul Chowdhury, M.D., Ph.D., Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Lydia Gilbert-McClain, M.D., Deputy Director, DPARP
Anthony Durmowicz, M.D., Clinical Team Leader, DPARP
Kimberly Witzmann, M.D., Clinical Reviewer, DPARP
Christine Chung, R.Ph., Program Coordinator, DPARP
Craig Bertha, Ph.D., Acting CMC Lead, Division of New Drug Quality Assessment III
Satjit Brar, Ph.D., Team Leader, Division of Clinical Pharmacology II (DCP II)
Dinko Rekic, Ph.D., Clinical Pharmacology Reviewer, DCP II
David Petullo, Ph.D., Team Leader, Division of Biometrics II (DBII)
Robert Abugov, Ph.D., Biometrics Reviewer, DBII
Lissa Owens, Pharm.D., Safety Evaluator, Division of Medication Error Prevention & Analysis

SPONSOR ATTENDEES:

Michael Golden, Senior Vice President, Regulatory Affairs and Quality
Tracy Fischer, Pharm.D., Senior Director, Regulatory Affairs
Shannon Strom, Ph.D., Director, Regulatory Affairs
Carmella Moody, Ph.D., Director Regulatory Affairs
Colin Reisner, M.D., Chief Medical Officer/Executive Vice President of Clinical Development
Patrick Darken, Ph.D., Vice President, Statistics
Andrea Maes, Ph.D., Associate Director, Biostatistics
Carlos Fernandez, M.D., Senior Medical Director, Head of Pharmacovigilance
Chad Orevillo, M.P.H, Vice President, Head of Medical Communications
Shahid Siddiqui, M.D., M.H.S.A, Senior Director, Clinical Development

BACKGROUND:

Pearl Therapeutics is developing GFF inhalation aerosol for long-term, twice daily maintenance treatment (b) (4) with COPD, including chronic bronchitis and emphysema. (b) (4) NDA (b) (4) planned via the 505(b)(2) pathway relying on the Agency's previous findings of safety with the reference listed drugs Foradil Aerolizer, Robinul, and Robinul Forte, and Robinul Injection. Pearl plans to file the NDA for the combination product GFF MDI in June 2015, (b) (4) A separate CMC pre-NDA meeting request will be submitted later this year.

The pre-NDA meeting request was submitted February 28, 2014, and the briefing package was received May 1, 2014. Clarifications to briefing package contents were received May 20, 2014 (see Attachment).

After review of the briefing package, FDA sent preliminary responses to Pearl's questions in an emailed letter dated May 28, 2014. In an email dated May 30, 2014, Pearl requested additional clarification and discussion of FDA response to Questions 1, 3, 6, 7, 8, 12, 14, and 19. Pearl's comments are incorporated into the body of the minutes as well as provided as an Attachment.

The content of the letter is printed below, with the sponsor's questions from the briefing package in *italics;* FDA's responses (meeting preliminary comments) in normal font; and Pearl's May 30, 2014, emailed responses also noted in *italics*. Summary of meeting discussions, if any, are found in **bold normal font** following the specific area of discussion.

QUESTIONS AND RESPONSES

Question 1

Does the Agency agree that change from baseline in morning pre-dose trough FEV1 (b) (4) *will provide a reasonable assessment of the treatment effects during chronic dosing?*

FDA response:

We do not agree. As discussed at the End-of-Phase 2 meeting held on December 21, 2012, we believe that the primary analysis should be at week 24, and an analysis of the treatment effect over 12 or 24 weeks may provide supportive data. Whether other products demonstrate tachyphylaxis or not is not informative to your GFF program.

Pearl's emailed response:

(b) (4)

(b) (4)

The Sponsor has measured FEV_1 AUC_{0-12} on Day 1 and at Week 12 in sub-studies of Study PT003006 and Study PT003007. These sub-studies are large enough to have been pivotal trials themselves (Study PT003006: N~700; Study PT003007: N~600). At Week 12, FEV_1 AUC_{0-12} was obtained in approximately 600 subjects in Study PT003006 and 500 subjects in Study PT003007. Each study is anticipated to provide approximately 160 subjects in the GFF MDI treatment arm, 135 subjects in the GP MDI and FF MDI treatment arms, and 65 subjects in the Placebo MDI treatment arm. (b) (4) (b) (4)

Discussion:

(b) (4)

(b) (4)

(b) (4) **The expectation for Pearl's 2-drug bronchodilation combination product (GFF) is that the combination wins on the lung function endpoint at 24-weeks, the contribution of each component is demonstrated, and an assessment of COPD exacerbations would trend in a positive direction (fewer COPD exacerbations).**

Pearl asked if (b) (4) **would be appropriate as the primary endpoint.**

FDA replied that the acceptable primary endpoint is trough FEV_1 at week 24.

(b) (4)

, an assessment of trough FEV_1 at 24 weeks is more appropriate. In addition, from a regulatory perspective, a clinical expectation for a LAMA/LABA combination

product is that even if the primary endpoint was FEV_1, the study would show some nominal improvement in COPD exacerbations. Therefore, the pivotal studies should be long enough to allow an evaluation of a trend toward improvement in exacerbations, which typically would be 24 weeks.

Question 2

Does the Agency agree with the planned approach to evaluate the robustness of the primary analysis to missing data for Studies PT003006 and PT003007?

FDA response:

Although the sensitivity analyses you proposed are valid methods, we do not agree with your primary analysis. Your sensitivity analyses should evaluate the treatment effect at Week 24, see response to Question 1.

As an additional sensitivity analysis, we suggest cumulative responder analyses for change from baseline trough FEV_1 at Week 24. Define patients who discontinue study treatment as having experienced an extremely low change from baseline FEV_1, i.e., as non-responders for all thresholds considered. Then create a cumulative distribution plot of the data for each treatment group for all possible response levels and evaluate the difference between the curves (J.T. Farrar, R. H. Dworkin, M. B. Max, Use of the Cumulative Proportion of Responders Analysis Graph to Present Pain Data Over a Range of Cut-Off Points: Making Clinical Trial Data More Understandable, Journal of Pain and Symptom Management, 31 (4) (2006), pp.369-377; Morton B. Brown, A Test for the Difference Between Two Treatments in a Continuous Measure of Outcome when there are Dropouts. Controlled Clinical Trials, 13 (1192), pp 213-225.)

Question 3

Does the Agency agree with the planned approach for the evaluation of laboratory parameters, vital signs, and electrocardiograms (ECGs) including:

a) The specified thresholds for defining potentially clinically significant (PCS) values in the clinical study reports (CSRs) for Studies PT003006, PT003007, and PT003008 and the ISS?

FDA response:

The thresholds used to define potentially clinically significant values as presented in Table 2.5 are reasonable. We appreciate your email received 5/21/2014, which clarifies that you propose to use CTCAE categories only for low potassium and low serum glucose values. We will otherwise expect your submission to include standard shift tables utilizing groupings based on values times the upper limits of normal (for example, within normal limits/ <2x ULN/ 2-3xULN, 3-5x ULN, >5x ULN, etc.) for changes from baseline across the treatment period.

Pearl's emailed response:

The comment in the email dated 5/21/2014 was specific to the Phase II Chronic-dosing Studies. For the integration of safety measures for the Phase II Chronic-dosing Studies, the shifts between baseline and post-baseline highest CTCAE 4.03 grade in the briefing document should have specified that only potassium and glucose were evaluated.

For the Phase III Studies, Pearl Therapeutics is planning on using CTCAE categories for all labs. Shift tables relative to the normal reference ranges will be produced using the categories defined by the CTCAE Version 4.03 grades. For these shift tables, subject's pre-dose grade will be cross-tabulated by the subject's maximum post-baseline grade for each treatment throughout the treatment period. In addition, the subject's maximum post-baseline grade during treatment will be tabulated for all baseline grades combined.

Pearl Therapeutics believes that CTCAE grades provide a standardized and consistent approach to defining and grading treatment related toxicity. Such a standardized approach provides a more detailed classification of lab abnormalities than establishing a pre-specified threshold (i.e., > x2 ULN) for all parameters under consideration. For example, if we consider sodium (reference range: 134-144 mEq/L), relatively small changes, e.g. 10-20 mmol/L above ULN would most likely result in hospitalization. Levels > 160 mmol/L are life threatening. For this electrolyte and many others, life threatening changes occur with values much lower than 2x ULN. A CTCAE grading will capture severity even when changes are well below a pre-specified threshold (2 x ULN as in the example discussed). Details regarding the specific severities for different lab abnormalities are provided in the table below.

Discussion:
FDA explained that the CTCAE is designed for cancer patients, the grading allowing more severe adverse effects. Although using CTCAE is acceptable, FDA may request additional data or analyses utilizing more conservative cutoff criteria. For example, the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, are more conservative. [Also reference page 3 and 4 (of 9) in Pearl's May 30, 2014, emailed responses provided in Attachment.]

b) The use of International System of Units (SI) for laboratory parameters?

FDA response:
Use of SI units is acceptable, provided that appropriate normal reference values are included.

Question 4
Does the Agency agree with the specified adverse events (AEs) of special interest for evaluation in the CSRs for Studies PT003006, PT003007, and PT003008 and the ISS?

FDA response:
Your proposed adverse events of special interest are reasonable.

Question 5
Pearl Therapeutics plans to provide narratives and eCRFs for all subjects with AEs leading to withdrawal, serious adverse events (SAEs), and deaths in the CSRs for Studies PT003006, PT003007, and PT003008.

a. Does the Agency agree with this approach?

FDA response:
Your proposed plan for narrative style and contents for all AEs leading to withdrawal, SAEs and deaths, is acceptable.

b. Does the Agency agree with the structure and level of detail provided in the example SAE narratives?

FDA response:
Your examples are reasonable; however, if questions arise for specific cases during the review period, we will send requests for information to clarify.

Question 6

The effects of intrinsic and extrinsic factors on the pharmacokinetics (PK) of glycopyrronium and formoterol are being evaluated on Day 1 and at Week 12 in a subset of subjects in Study PT003006. Does the Agency agree with the proposed intrinsic and extrinsic factors for evaluation?

FDA response:
Your proposal is insufficient. Extrinsic and intrinsic factor's influence on the pharmacokinetics of drugs should be explored on primary pharmacokinetic parameters (e.g., CL/F, Vc, Vp). In addition, secondary pharmacokinetic parameters and measures of exposure (e.g., Half-life, AUC, Cmax) may be used to illustrate final parameter-covariate relationships. Primary pharmacokinetic parameters should be estimated using appropriate methodology, e.g., population pharmacokinetic modeling.

With respect to the intrinsic and extrinsic factors being explored, you should include creatinine clearance in the covariate analysis of both formoterol and glycopyrronium. In addition, the influence of hepatic impairment on primary pharmacokinetic parameters should be investigated provided your study includes such patients. We encourage you to explore all covariate-parameter relationships, linear and non-linear, that are physiologically plausible.

You may utilize sparse sampling with only a few samples per subject, rich sampling with full concentration-time profiles per subject, or a combination of both types of sampling strategies. More information about sampling strategy and covariate analysis is available in the population PK guidance.
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072137.pdf

Your analysis plan states that concentrations below the limit of quantification (LOQ) will be set to zero. This approach may introduce bias. You should either ignore (set to missing) the concentrations below LOQ or, if found pharmacokinetically plausible, set them to a value of ½ LOQ.

Pearl's emailed response:
In addition to a non-compartmental PK analysis in Study PT003006, Pearl Therapeutics will perform a population PK analysis as per FDA guidance on glycopyrronium and formoterol based on data collected in Study PT0050801, Study PT005003, Study PT0010801, Study PT0031002 and Study PT003006. This dataset will include a total of approximately 370 subjects with COPD and provide a robust understanding of intrinsic and extrinsic sources of variability on PK parameters. Concentrations below the LOQ will be handled as recommended above for the population PK analysis. Additional details regarding the population PK methodology and LOQ handling will be described in an analysis plan.

As suggested by the Agency, Pearl Therapeutics will include creatinine clearance as a covariate for both formoterol and glycopyrronium. Please note that subjects with clinically relevant hepatic impairment were excluded from the Phase III clinical studies (Subjects with abnormal liver function tests defined as AST, ALT, or total bilirubin ≥ 1.5 times upper limit of normal were excluded.). Pearl Therapeutics anticipates that GFF MDI will have a similar precautionary statement to Symbicort Inhalation Aerosol regarding use in patients with hepatic impairment.

Discussion:
FDA stated that Pearl's proposed plan for analysis and data collection is adequate. They clarified that regardless of the type of PK analysis method employed, the sponsor should not set LOQ concentration to zero, as it will introduce bias. The missing PK observation should be set to "missing" or allocated a value of ½ the LOQ. The submitted datasets should flag the values that are considered LOQ.

In addition, FDA pointed out that the results from the population PK analysis would be of more importance to the clinical pharmacology review rather than the NCA analysis.

Question 7
Pearl Therapeutics has a single SAP for the two 24-week pivotal studies (Studies PT003006 and PT003007) and a separate SAP for the 28-week extension study (Study PT003008). Does the Agency have any comments on the analyses proposed in the draft SAPs?

FDA response:
Except for event based endpoints, such as exacerbations and use of rescue medications, efficacy for studies PT003006 and PT003007 should be measured at landmark, on a single study day or week (b) (4) See our response to Question 1.

Since new exacerbations cannot occur during an extant exacerbation, the offset term for each patient in your Poisson regression model should exclude the summed duration of exacerbations during the reporting period. Also, if exacerbations occurring in close sequence are to be combined into a single exacerbation, prespecify a time-based criterion by which they are to be merged. For example, if exacerbations which occur within 'x' days of each other are to be merged into a single exacerbation, the offset term for each patient should exclude the 'x' days following termination of each exacerbation.

Regarding control of Type 1 error with multiple endpoints, you propose to evaluate the statistical significance of treatment differences using the Hochberg procedure, which may

be sensitive to lack of independence between the endpoints tested. Instead, we recommend that you consider using either a Holm procedure or a Bonferroni procedure, with the Holm procedure truncated if allocating type-I error to subsequent families in the testing hierarchy. Further, ensure that your statistical testing procedures include provisions to control Type 1 error over all efficacy endpoints being considered for inclusion on the product label.

That study PT003008 is not adequately controlled will preclude its use for analyses of efficacy.

Pearl's emailed response:
Pearl Therapeutics would like to clarify the Agency's position on the analysis of secondary and other efficacy measures included in the pivotal trials. (b) (4)

Regarding exacerbations, the current approach as summarized in the SAPs for Study PT003006/PT003007 and Study PT003008 relies on the Principal Investigators or designee to determine when events are distinct and simply requires that they do not overlap. Would the Agency prefer that the Sponsor require a certain number of days between exacerbations in order to consider them separate events in the analysis, for example 5 days?

It is Pearl Therapeutics' understanding that the Hochberg test is only anti-conservative in the unlikely case of discordant treatment effects on correlated endpoints included in the procedure for Studies PT003006 and PT003007. In addition, Type I errors are highly unlikely since glycopyrronium and formoterol fumarate have been shown to be effective in the treatment of COPD in multiple studies with other formulations, as well as in Phase II studies with Pearl Therapeutics' formulation. If there is no evidence of discordant treatment effects in the results, would the Agency still be concerned about the use of Hochberg to control type I error within each treatment comparison?

(b) (4)

Discussion:
FDA noted that the 24 week endpoints in studies 3006 and 3007 will provide adequate information for maintenance of efficacy but that evaluation of the 52 week efficacy endpoint in study 3008 which includes open-label data may provide little or no useful additional efficacy information. Additional points were discussed:

a. The primary endpoint should be at the 52 week landmark (b) (4)

b. Regarding missing data, see our recommendations for studies 3006 and 3007.

c. You note that 'since the primary objective of the trial is the evaluation of safety, no additional controls of Type I error are planned.' Lack of control of Type 1 error will pose a review issue.

d. (b) (4)

e. Regardless of whether week 52 results provide additional information, a single study may not suffice for additional label claims.

f. Set a protocol-specified definition for time between exacerbations (such as 7-10 days) by which to consider them separate events; it will be helpful in providing consistency and decrease variability in counting of exacerbations and determination of associated offsets.

g. Appropriateness of pooling data and patients from studies 3006 and 3007 into study 3008 will be contingent on:

1) Similarity of results from both studies 3006 and 3007,
2) Lack of impact on randomization of patient withdrawal. For example, show that results from week 12 and 24 endpoints from ITT populations in studies 3006 and 3007 are similar to those of the ITT population enrolled for study 3008.

Question 8

Pearl Therapeutics has included a sample dataset package for Study PT003006. The dataset packages for Studies PT003007 and PT003008 will be similar.

a) Does the Agency agree with the structure and content of the sample dataset package for Study PT003006?

FDA response:

Unfortunately, we were unable to read your adam-define.xml file. However, for each efficacy observation in your analysis datasets, ensure that you provide a variable or variables to indicate whether the data was observed at the associated time point. And, if the data was missing at that time point and imputed, indicate the type of imputation used in its derivation.

Further, ensure that you provide all macros, formats, and programs used to analyze disposition and efficacy.

Pearl's emailed response:

The ADaM define.xml file should open in Internet Explorer as long as the companion file define2-0-0.xsl is in the same directory. Please provide further detail concerning the trouble you are experiencing while opening or reading the file. Would it be possible for Pearl Therapeutics to resend the files (define.xml, define2-0-0.xsl) and receive feedback from the Agency in the meeting minutes?

There is a separate ADaM data set for efficacy data without imputation (ADEFF) and efficacy data with imputation (ADEFFMI). Within ADEFF, the CRIT1 – CRIT5 and CRIT1FL- CRIT5FL variables provide detail concerning the nature of any missing data. The variables within ADEFFMI provide detail concerning the data imputation under the pattern

mixture models framework as outlined in the SAPs for Study PT003006/PT003007 and Study PT003008.

Pearl Therapeutics plans to only provide the macros, formats and programs for the statistical analysis of disposition and primary and secondary efficacy endpoints for Studies PT003006, PT003007 and PT003008. Is this acceptable to the Agency?

Discussion:
FDA responded that Pearl's proposal is generally acceptable, however, it depends on result from 3008, and additional data may be requested.

Post-meeting note:
Regarding the adam-define.xml file, FDA sent an email on June 4, 2014, with an attachment showing how the data file output appeared on Internet Explorer. FDA will work with the sponsor to resolve the problem.

b) *Would the Agency prefer the use of the Respiratory System Findings (RE) and Procedure Agents (AG) domains from the draft Clinical Data Interchange Standards Consortium (CDISC) Asthma Therapeutic Area Data Standards?*

FDA response:
Use of these domains is at your discretion.

Question 9
Does the Agency agree with the approach for the pooling of data from the two 24-week pivotal studies (Studies PT003006 and PT003007) in the ISE and the ISS and the pooling of data from Studies PT003006, PT003007, and PT003008 in the CSR for Study PT003008, with references where appropriate in the ISE and the ISS?

FDA response:
Your proposal to pool data for the ISS and ISE is at your discretion and appears reasonable; however, the determination of efficacy will be based upon individual endpoint analysis from each of your replicate studies, not from pooled ISE results.

Question 10
Does the Agency agree with the proposed study groupings, efficacy analyses, subgroup analyses, and table of contents for the ISE?

FDA response:
While it is your prerogative to display data within the ISE as you wish, we reiterate that we do not agree with your proposed efficacy analyses; refer to responses to Questions 1 and 7. Your proposed subgroup categories appear reasonable, as do the general outline plans for your anticipated ISE.

Question 11
Does the Agency agree with the proposed study groupings, safety analyses [including the proposed analysis for major adverse cardiac events (MACE)], subgroup analyses and table of contents for the ISS?

FDA response:
Your proposals appear reasonable.

Question 12

Pearl Therapeutics plans to display and summarize all data for the comparison of GP MDI versus Placebo MDI in the ISE and ISS planned for the GFF MDI NDA. (b) (4)

FDA response:

(b) (4)

Pearl's emailed response:

(b) (4)

Discussion:

(b) (4)

Question 13

Pearl Therapeutics is completing a Human Factors (HF) Formative Evaluation (design verification) and will provide the complete assessment in the GFF MDI NDA demonstrating conformance with established modern principles and practices of HF Engineering. In addition, Pearl Therapeutics is evaluating the accuracy, reliability, and functionality of the dose indicator in subjects in the Phase III clinical program that is evaluating the efficacy and safety of GFF MDI. Based on these assessments, the fact that the MDI Device used for GFF MDI is a standard device that is used in other approved products and the device has been effectively used in clinical studies using similar Patient Use Instructions as approved products, Pearl Therapeutics does not plan to perform a label comprehension and usability study. Does the Agency agree with this approach? Are there any specific issues for HF Analysis for an MDI device that the Agency suggests are important to include other than the studies listed below?

FDA response:
Your approach sounds reasonable. We do not have additional comments and/or recommendations at this time.

Question 14

(b) (4)

[redacted]

FDA response:
Your NDA submission should be complete at the time of submission. As such, dose-ranging and dose-interval data should be included within the original NDA submission. While serial spirometry curves are frequently included in the prescribing information for bronchodilator products, the contents of final labeling will be determined during the NDA review.

Pearl's emailed response:
The dose ranging and dose interval data have been completed and were discussed with the Agency at the EOP2 Meeting. These data will be included in the NDA. The 6 month pivotal studies included serial spirometry in a subset of patients, with approximately 700 subjects in Study PT003006 and 600 subjects in Study PT003007.

(b) (4)

[redacted]

Discussion:
Given the bronchodilator indication, FDA commented about the utility of conducting a study for results that would already be known (pending approval of GFF as a bronchodilator) - that GFF would be an effective bronchodilator when given at 12 hour dosing intervals.

(b) (4)

[redacted]

Question 15

(b) (4)

[redacted]

FDA response:

(b) (4)

Question 16

As previously discussed with the Agency, Pearl Therapeutics plans to file a 505(b)(2) NDA using Robinul® Injection (NDA 017558) as the reference listed product for glycopyrronium. Does the Agency agree that no patent certification is necessary, as described in 21 CFR Section 314.50(i)(1)(ii), as there are no unexpired patents for Robinul Injection listed in the Orange Book?

FDA response:

As per 21 CFR Section 314.50 (i)(1)(i), a 505(b)(2) application is required to provide applicable patent certification(s). As an example, if there are no unexpired patents, provide Paragraph II Certification.

Question 17

Pearl Therapeutics is now an AstraZeneca group company. As a result of the acquisition, Pearl Therapeutics now has a right of reference to the nonclinical studies conducted with formoterol fumarate to support the approval of Symbicort Inhalation Aerosol (NDA 021929) and no longer needs to utilize Foradil Aerolizer as a reference listed drug. Does the Agency agree with the approach of referencing the nonclinical studies conducted with formoterol fumarate in NDA 021929 (Symbicort Inhalation Aerosol) to support the approval of GFF MDI?

FDA response:

This is reasonable.

Question 18

Can the Agency provide guidance on the following aspects of the GFF MDI target product profile (TPP)?

a) Assuming the Phase III efficacy data are positive, does the Agency agree that an indication as a "long-term, maintenance (b) (4) *treatment for airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema" could be supported for GFF MDI?*

FDA response:

While your plans appear reasonable, any labeling decisions will be a review issue.

b) As the GFF MDI label will differ substantially from the Robinul Injection label, Pearl Therapeutics does not plan to include an annotated label comparison to the Robinul Injection label in the NDA. Does the Agency agree this approach?

FDA response:
While your plans appear reasonable, any labeling decisions will be a review issue.

c) Does the Agency agree with the wording of the proposed black box warning for GFF MDI?

FDA response:
Labeling decisions will be a review issue.

d) Does the Agency agree if no evidence of adverse effects between cardioselective betablockers and GFF MDI are observed in the Phase III clinical studies, that the warning regarding concomitant use of beta blockers with GFF MDI in Section 7.5 can be omitted or revised based on the data from the Phase III clinical studies?

FDA response:
Labeling decisions will be a review issue.

e) Does the Agency agree with the approach for developing the Instructions for Administering GFF MDI in Section (b) (4)

FDA response:
Labeling decisions will be a review issue.

Question 19
During a telephone call on 18 April 2014 with Christine Chung, R.Ph., FDA Regulatory Project Manager, Pearl Therapeutics was informed that the Agency has changed their decision and would like Pearl Therapeutics to change the naming convention of glycopyrronium back to glycopyrrolate for (b) (4) *GFF MDI. Pearl Therapeutics would like to ask the Agency to reconsider their decision.*

FDA response:
We have reconsidered this issue and discussed it internally. Use "glycopyrrolate" as the established name for the drug product and base the strength on the salt.

Pearl's emailed response:
Based on the Agency's written feedback dated 14 May 2013, Pearl Therapeutics has used "glycopyrronium" in all documentation. Pearl Therapeutics acknowledges the Agency's change in position and the requirement to use "glycopyrrolate" as the established name for the drug product and to base the strength on the salt. Pearl Therapeutics will use "glycopyrrolate" as the established name in the labeling of the drug product; however, all other NDA documents will use "glycopyrronium". Is this acceptable to the Agency?

Discussion:
USP has made a decision that glycopyrrolate will be used instead of glycopyrronium, and the USAN Council has denied a USAN request for glycopyrronium. Taking into account those decisions, FDA responded that Pearl's proposal is acceptable, however, expressed concerns with how specifications for the

drug substance and drug product would be presented within the application submission. They recommended that the sponsor provide good footnotes for conversion in the specifications as well as in the methods, being clear what is being assayed.

PREA REQUIREMENTS

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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

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

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

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

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

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

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

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

ISSUES REQUIRING FURTHER DISCUSSION:

There were no issues requiring further discussion.

ATTACHMENTS (in order of appearance):

- Pearl's emailed clarifications to briefing package contents emailed May 20, 2014 (2).
- Pearl's May 30, 2014, emailed responses and request for clarification to FDA meeting preliminary comments.

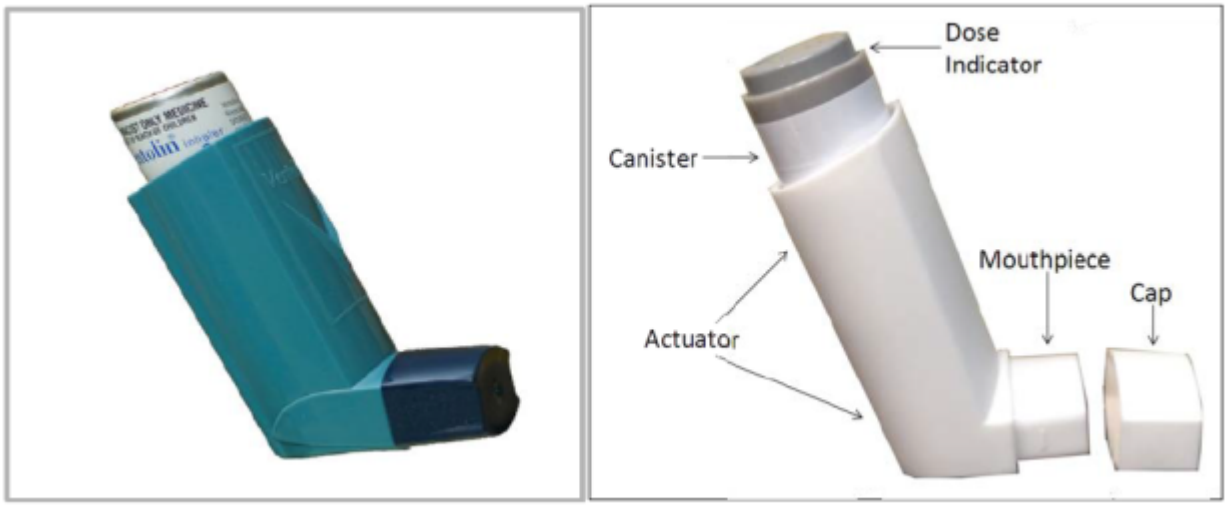
Chung, Christine

From: Tracy Fischer <tfischer@pearltherapeutics.com>
Sent: Tuesday, May 20, 2014 8:09 PM
To: Chung, Christine
Subject: IND 107739 Pre-NDA Meeting Briefing Document
Attachments: emfalert.txt

Hi Christine,

Below is a response to the issue you raised this morning regarding Question 13 of the Pre-NDA Briefing Document. Sorry for not getting this to you sooner. Please let me know if you need anything else.

Pearl Therapeutics intended for the statement in Question 13 "*the MDI Device used for GFF MDI is a standard device that is used in other approved products*" to convey that GFF MDI is similar to other approved metered dose inhaler (MDI) products (e.g. Ventolin® HFA Inhalation Aerosol, Advair® HFA Inhalation Aerosol, Symbicort® Inhalation Aerosol, Alvesco® Inhalation Aerosol) in that it is a standard press and breathe MDI with a canister, valve, actuator, mouthpiece and dose indicator/counter. A photograph of Ventolin® HFA Inhalation Aerosol and a drawing of Pearl Therapeutics GFF MDI are provided below for reference. The valve, actuator, (b) (4) canister, and dose indicator suppliers for GFF MDI have confirmed that the materials used in the container closure system components are or have been used in US-approved MDI products (although not necessarily in the same combination, e.g., a different can volume being used with a common valve and actuator type). Due to confidentially reasons, the suppliers are unable to provide the specific US-approved MDI products that contain the components used in GFF MDI.



Kind Regards,
Tracy

Tracy Fischer, Pharm.D.
Senior Director, Regulatory Affairs
Pearl Therapeutics, Inc.
200 Saginaw Drive
Redwood City, CA 94063
phone: 650-305-2631

Chung, Christine

From: Tracy Fischer <tfischer@pearltherapeutics.com>
Sent: Tuesday, May 20, 2014 10:04 PM
To: Chung, Christine
Subject: IND 107739 Pre-NDA Briefing Document
Attachments: emfalert.txt

Hi Christine,

In advance of the internal Agency meeting tomorrow I wanted to make you aware of a small error that we found in the pre-NDA Briefing Document on page 64 (Section 2.1.11.1.3). For the integration of safety measures for the Phase II Chronic-dosing Studies the shifts between baseline and post-baseline highest CTCAE 4.03 grade should have specified that only potassium and glucose were evaluated.

Thanks,
Tracy

Tracy Fischer, Pharm.D.
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Pearl Therapeutics would like to discuss Questions 1, 3, 6, 7, 8, 12, 14, and 19. A summary of the specific items within each question that Pearl Therapeutics would like to discuss is provided below. Please note that the questions are in bold italics and FDA responses are in bold font.

Question 1

Does the Agency agree that change from baseline in morning pre-dose trough FEV1 (b) (4) ***will provide a reasonable assessment of the treatment effects during chronic dosing?***

FDA response

We do not agree. As discussed at the End-of-Phase 2 meeting held on December 21, 2012, we believe that the primary analysis should be at week 24, and an analysis of the treatment effect over 12 or 24 weeks may provide supportive data. Whether other products demonstrate tachyphylaxis or not is not informative to your GFF program.

Clarification from Pearl Therapeutics

(b) (4)

The Sponsor has measured FEV_1 AUC_{0-12} on Day 1 and at Week 12 in sub-studies of Study PT003006 and Study PT003007. These sub-studies are large enough to have been pivotal trials themselves (Study PT003006: N~700; Study PT003007: N~600). At Week 12, FEV_1 AUC_{0-12} was obtained in approximately 600 subjects in Study PT003006 and 500 subjects in Study PT003007. Each study is anticipated to provide approximately 160 subjects in the GFF MDI treatment arm, 135 subjects in the GP MDI and FF MDI treatment arms, and 65 subjects in the Placebo MDI treatment arm. (b) (4)

(b) (4)

Question 3

Does the Agency agree with the planned approach for the evaluation of laboratory parameters, vital signs, and electrocardiograms (ECGs) including:

a) The specified thresholds for defining potentially clinically significant (PCS) values in the clinical study reports (CSRs) for Studies PT003006, PT003007, and PT003008 and the ISS?

FDA response:

The thresholds used to define potentially clinically significant values as presented in Table 2.5 are reasonable. We appreciate your email received 5/21/2014, which clarifies that you propose to use CTCAE categories only for low potassium and low serum glucose values. We will otherwise expect your submission to include standard shift tables utilizing groupings based on values times the upper limits of normal (for example, within normal limits/ <2x ULN/ 2-3xULN, 3-5x ULN, >5x ULN, etc.) for changes from baseline across the treatment period.

b) The use of International System of Units (SI) for laboratory parameters?

FDA response:

Use of SI units is acceptable, provided that appropriate normal reference values are included.

Clarification from Pearl Therapeutics

The comment in the email dated 5/21/2014 was specific to the Phase II Chronic-dosing Studies. For the integration of safety measures for the Phase II Chronic-dosing Studies, the shifts between baseline and post-baseline highest CTCAE 4.03 grade in the briefing document should have specified that only potassium and glucose were evaluated.

For the Phase III Studies, Pearl Therapeutics is planning on using CTCAE categories for all labs. Shift tables relative to the normal reference ranges will be produced using the categories defined by the CTCAE Version 4.03 grades. For these shift tables, subject's pre-dose grade will be cross-tabulated by the subject's maximum post-baseline grade for each treatment throughout the treatment period. In addition, the subject's maximum post-baseline grade during treatment will be tabulated for all baseline grades combined.

Pearl Therapeutics believes that CTCAE grades provide a standardized and consistent approach to defining and grading treatment related toxicity. Such a standardized approach provides a more detailed classification of lab abnormalities than establishing a pre-specified threshold (i.e., > x2 ULN) for all parameters under consideration. For example, if we consider sodium (reference range: 134-144 mEq/L), relatively small changes, e.g. 10-20 mmol/L above ULN would most likely result in hospitalization. Levels > 160 mmol/L are life threatening. For this electrolyte and many others, life threatening changes occur with values much lower than 2x ULN. A CTCAE grading will capture severity even when changes are well below a pre-specified threshold (2 x ULN as in the example discussed). Details regarding the specific severities for different lab abnormalities are provided in the table below.

Common Terminology Criteria for Adverse Events (CTCAE) 4.03 Grades

	CTCAE Grade I	CTCAE Grade II	CTCAE Grade III	CTCAE Grade IV	Reference Range
Hematology					
Anemia	LLN-10 g/dL	<10.0-8.0 g/dL	<80 g/dL	Life-threatening consequences	Female 11.5-15 g/dL; Male 12.5-17 g/dL
Hemoglobin increased	Hemoglobin increased	Increase in >0 - 2 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >4 gm/dL above ULN or above baseline if baseline is above ULN	
White Blood Cell count with differential	Leukocytosis (White blood cell increased)	>ULN - 40,000/mm^3	40,000 - 100,000/mm^3	>100,000/mm^3	4-10.5 10^3/uL
White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	
Liver Enzymes and Other Function Tests					
Alkaline phosphatase	> ULN-2.5 x ULN	>2.5-5.0 x ULN	>5.0-20.0 x ULN	>20.0 x ULN	25-150 IU/L
AST (U/L)	> ULN-3.0 x ULN	>3.0-5.0 x ULN	>5.0-20.0 x ULN	>20.0 x ULN	0-40
ALT (U/L)	> ULN-3.0 x ULN	>3.0-5.0 x ULN	>5.0-20.0 x ULN	>20.0 x ULN	Female 0-32 IU/L; Male 0-44 IU/L
GGT (U/L)	> ULN-2.5 x ULN	>2.5-5.0 x ULN	>5.0-20.0 x ULN	>20.0 x ULN	Female 0-60 IU/L; Male 0-65 IU/L
Total Bilirubin	> ULN-1.5 x ULN	>1.5-3.0 x ULN	>3.0-10.0 x ULN	>10.0 x ULN	0.1-1.2 mg/dL
Other Clinical Blood Chemistry					
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL	Corrected serum calcium of >11.5 - 12.5 mg/dL	Corrected serum calcium of >12.5 - 13.5 mg/dL	Corrected serum calcium of >13.5 mg/dL	8.5-10.6 mg/dL
Hyperglycemia	Fasting glucose value >ULN -160 mg/dL	Fasting glucose value >160 - 250 mg/dL	>250 - 500 mg/dL	>500 mg/dL	65-59 mg/dL
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L	>7.0 mmol/L;	3.5-5.5 mEq/L
Hypermagnesemia	>ULN - 3.0 mg/dL	n/a	>3.0 - 8.0 mg/dL	>8.0 mg/dL; life-threatening consequences	1.6-2.6 mg/dL
Hypernatremia (Sodium Increased)	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences	134-144 mEq/L
Hypoalbuminemia (Albumin Decreased)	<LLN - 3 g/dL	<3 - 2 g/dL	<2 g/dL	Life-threatening consequences; urgent intervention indicated	3.2 - 5 g/dL

Common Terminology Criteria for Adverse Events (CTCAE) 4.03 Grades

	CTCAE Grade I	CTCAE Grade II	CTCAE Grade III	CTCAE Grade IV	Reference Range
Hypocalcemia (Calcium Decreased)	<LLN - 8.0 mg/dL	<8.0 - 7.0 mg/dL	<7.0 - 6.0 mg/dL	<6.0 mg/dL	8.5-10.6 mg/dL
Hypoglycemia (Glucose Decreased)	<LLN - 55 mg/dL	<55 - 40 mg/dL	<40 - 30 mg/dL	<30 mg/dL	65-59 mg/dL
Hypokalemia (Potassium Decreased)	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L	<3.0 - 2.5 mmol/L	<2.5 mmol/L	3.5-5.5 mEq/L
Hypomagnesemia (Magnesium Decreased)	<LLN - 1.2 mg/dL	<1.2 - 0.9 mg/dL	<0.9 - 0.7 mg/dL	<0.7 mg/dL	1.6-2.6 mg/dL
Hyponatremia (Sodium Decreased)	<LLN - 130 mmol/L		<130 - 120 mmol/L	<120 mmol/L	134-144 mEq/L
Hypophosphatemia (Phosphate Decreased)	<LLN - 2.5 mg/dL	<2.5 - 2.0 mg/dL	<2.0 - 1.0 mg/dL	<1.0 mg/dL	2.5-4.5 mg/dL

Question 6

The effects of intrinsic and extrinsic factors on the pharmacokinetics (PK) of glycopyrronium and formoterol are being evaluated on Day 1 and at Week 12 in a subset of subjects in Study PT003006. Does the Agency agree with the proposed intrinsic and extrinsic factors for evaluation?

FDA response:

Your proposal is insufficient. Extrinsic and intrinsic factor's influence on the pharmacokinetics of drugs should be explored on primary pharmacokinetic parameters (e.g., CL/F, Vc, Vp). In addition, secondary pharmacokinetic parameters and measures of exposure (e.g., Half-life, AUC, Cmax) may be used to illustrate final parameter-covariate relationships. Primary pharmacokinetic parameters should be estimated using appropriate methodology, e.g., population pharmacokinetic modeling.

With respect to the intrinsic and extrinsic factors being explored, you should include creatinine clearance in the covariate analysis of both formoterol and glycopyrronium. In addition, the influence of hepatic impairment on primary pharmacokinetic parameters should be investigated provided your study includes such patients. We encourage you to explore all covariate-parameter relationships, linear and non-linear, that are physiologically plausible.

You may utilize sparse sampling with only a few samples per subject, rich sampling with full concentration-time profiles per subject, or a combination of both types of sampling strategies. More information about sampling strategy and covariate analysis is available in the population PK guidance.
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072137.pdf

Your analysis plan states that concentrations below the limit of quantification (LOQ) will be set to zero. This approach may introduce bias. You should either ignore (set to missing) the concentrations below LOQ or, if found pharmacokinetically plausible, set them to a value of ½ LOQ.

Clarification from Pearl Therapeutics

In addition to a non-compartmental PK analysis in Study PT003006, Pearl Therapeutics will perform a population PK analysis as per FDA guidance on glycopyrronium and formoterol based on data collected in Study PT0050801, Study PT005003, Study PT0010801, Study PT0031002 and Study PT003006. This dataset will include a total of approximately 370 subjects with COPD and provide a robust understanding of intrinsic and extrinsic sources of variability on PK parameters. Concentrations below the LOQ will be handled as recommended above for the population PK analysis. Additional details regarding the population PK methodology and LOQ handling will be described in an analysis plan.

As suggested by the Agency, Pearl Therapeutics will include creatinine clearance as a covariate for both formoterol and glycopyrronium. Please note that subjects with clinically relevant hepatic impairment were excluded from the Phase III clinical studies (Subjects with

abnormal liver function tests defined as AST, ALT, or total bilirubin ≥ 1.5 times upper limit of normal were excluded.). Pearl Therapeutics anticipates that GFF MDI will have a similar precautionary statement to Symbicort Inhalation Aerosol regarding use in patients with hepatic impairment.

Question 7

Pearl Therapeutics has a single SAP for the two 24-week pivotal studies (Studies PT003006 and PT003007) and a separate SAP for the 28-week extension study (Study PT003008). Does the Agency have any comments on the analyses proposed in the draft SAPs?

FDA response:

Except for event based endpoints, such as exacerbations and use of rescue medications, efficacy for studies PT003006 and PT003007 should be measured at landmark, on a single study day or week (b) (4) **See our response to Question 1.**

Since new exacerbations cannot occur during an extant exacerbation, the offset term for each patient in your Poisson regression model should exclude the summed duration of exacerbations during the reporting period. Also, if exacerbations occurring in close sequence are to be combined into a single exacerbation, prespecify a time-based criterion by which they are to be merged. For example, if exacerbations which occur within 'x' days of each other are to be merged into a single exacerbation, the offset term for each patient should exclude the 'x' days following termination of each exacerbation.

Regarding control of Type 1 error with multiple endpoints, you propose to evaluate the statistical significance of treatment differences using the Hochberg procedure, which may be sensitive to lack of independence between the endpoints tested. Instead, we recommend that you consider using either a Holm procedure or a Bonferroni procedure, with the Holm procedure truncated if allocating type-I error to subsequent families in the testing hierarchy. Further, ensure that your statistical testing procedures include provisions to control Type 1 error over all efficacy endpoints being considered for inclusion on the product label.

That study PT003008 is not adequately controlled will preclude its use for analyses of efficacy.

Clarification from Pearl Therapeutics

Pearl Therapeutics would like to clarify the Agency's position on the analysis of secondary and other efficacy measures included in the pivotal trials. (b) (4)

Regarding exacerbations, the current approach as summarized in the SAPs for Study PT003006/PT003007 and Study PT003008 relies on the Principal Investigators or designee to determine when events are distinct and simply requires that they do not overlap. Would the Agency prefer that the Sponsor require a certain number of days between exacerbations in order to consider them separate events in the analysis, for example 5 days?

It is Pearl Therapeutics' understanding that the Hochberg test is only anti-conservative in the unlikely case of discordant treatment effects on correlated endpoints included in the procedure for Studies PT003006 and PT003007. In addition, Type I errors are highly unlikely since glycopyrronium and formoterol fumarate have been shown to be effective in the treatment of COPD in multiple studies with other formulations, as well as in Phase II studies with Pearl Therapeutics' formulation. If there is no evidence of discordant treatment effects in the results, would the Agency still be concerned about the use of Hochberg to control type I error within each treatment comparison?

(b) (4)

Question 8

Pearl Therapeutics has included a sample dataset package for Study PT003006. The dataset packages for Studies PT003007 and PT003008 will be similar.

a) Does the Agency agree with the structure and content of the sample dataset package for Study PT003006?

FDA response:

Unfortunately, we were unable to read your adam-define.xml file. However, for each efficacy observation in your analysis datasets, ensure that you provide a variable or variables to indicate whether the data was observed at the associated time point. And, if the data was missing at that time point and imputed, indicate the type of imputation used in its derivation. Further, ensure that you provide all macros, formats, and programs used to analyze disposition and efficacy.

b) Would the Agency prefer the use of the Respiratory System Findings (RE) and Procedure Agents (AG) domains from the draft Clinical Data Interchange Standards Consortium (CDISC) Asthma Therapeutic Area Data Standards?

FDA response:

Use of these domains is at your discretion.

Clarification from Pearl Therapeutics

The ADaM define.xml file should open in Internet Explorer as long as the companion file define2-0-0.xsl is in the same directory. Please provide further detail concerning the trouble you are experiencing while opening or reading the file. Would it be possible for Pearl Therapeutics to resend the files (define.xml, define2-0-0.xsl) and receive feedback from the Agency in the meeting minutes?

There is a separate ADaM data set for efficacy data without imputation (ADEFF) and efficacy data with imputation (ADEFFMI). Within ADEFF, the CRIT1 – CRIT5 and CRIT1FL- CRIT5FL variables provide detail concerning the nature of any missing data. The variables within ADEFFMI provide detail concerning the data imputation under the pattern mixture models framework as outlined in the SAPs for Study PT003006/PT003007 and Study PT003008.

Pearl Therapeutics plans to only provide the macros, formats and programs for the statistical analysis of disposition and primary and secondary efficacy endpoints for Studies PT003006, PT003007 and PT003008. Is this acceptable to the Agency?

Question 12

Pearl Therapeutics plans to display and summarize all data for the comparison of GP MDI versus Placebo MDI in the ISE and ISS planned for the GFF MDI NDA. (b) (4)

FDA response:

(b) (4)

Clarification from Pearl Therapeutics

(b) (4)

Question 14

(b) (4)

FDA response:

Your NDA submission should be complete at the time of submission. As such, dose-ranging and dose-interval data should be included within the original NDA submission. While serial spirometry curves are frequently included in the prescribing information for bronchodilator products, the contents of final labeling will be determined during the NDA review.

Clarification from Pearl Therapeutics

The dose ranging and dose interval data have been completed and were discussed with the Agency at the EOP2 Meeting. These data will be included in the NDA. The 6 month pivotal studies included serial spirometry in a subset of patients, with approximately 700 subjects in Study PT003006 and 600 subjects in Study PT003007.

(b) (4)

Question 19

During a telephone call on 18 April 2014 with Christine Chung, R.Ph., FDA Regulatory Project Manager, Pearl Therapeutics was informed that the Agency has changed their decision and would like Pearl Therapeutics to change the naming convention of glycopyrronium back to glycopyrrolate for (b) (4) ***GFF MDI. Pearl Therapeutics would like to ask the Agency to reconsider their decision.***

FDA response:

We have reconsidered this issue and discussed it internally. Use "glycopyrrolate" as the established name for the drug product and base the strength on the salt.

Clarification from Pearl Therapeutics

Based on the Agency's written feedback dated 14 May 2013, Pearl Therapeutics has used "glycopyrronium" in all documentation. Pearl Therapeutics acknowledges the Agency's change in position and the requirement to use "glycopyrrolate" as the established name for the drug product and to base the strength on the salt. Pearl Therapeutics will use "glycopyrrolate" as the established name in the labeling of the drug product; however, all other NDA documents will use "glycopyrronium". Is this acceptable to the Agency?

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

/s/

CHRISTINE H CHUNG
07/01/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 107739

MEETING MINUTES

Pearl Therapeutics, Inc.
200 Saginaw Dr.
Redwood City, CA 94063

Attention: Tracy Fischer, Pharm.D.
Senior Director, Regulatory Affairs

Dear Dr. Fischer:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for glycopyrrolate and formoterol fumarate inhalation aerosol (GFF MDI).

We also refer to the meeting between representatives of your firm and the FDA on December 21, 2012. The purpose of the meeting was to discuss your phase 3 program and plans for the NDA submission.

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 me at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Christine Chung, R.Ph.
CDR, U.S. Public Health Service
Program Coordinator
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	End of Phase 2 (EOP2)
Meeting Date and Time:	December 21, 2012 1:00 – 2:30 P.M.
Meeting Location:	White Oak Building 22, Conference Room: 1417
Application Number:	IND 107739
Product Name:	Glycopyrrolate/formoterol fumarate inhalation aerosol (GFF MDI)
Indication:	COPD
Sponsor/Applicant Name:	Pearl Therapeutics, Inc.
Meeting Chair:	Badrul A. Chowdhury, Director
Meeting Recorder:	Christine Chung, Regulatory Project Manager

FDA ATTENDEES:

Badrul A. Chowdhury, M.D., Ph.D., Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Theresa Michele, M.D., Clinical Team Leader, DPARP
Robert Lim, M.D., Clinical Reviewer, DPARP
Marcie Wood, Ph.D., Pharmacology/Toxicology Team Leader (Acting), DPARP
Christine Chung, R.Ph., Regulatory Project Manager, DPARP
Prasad Peri, Ph.D., Branch Chief, Division of New Drug Quality Assessment (DNDQA) Branch VIII
Alan Schroeder, Ph.D., CMC Lead, DNDQA III
Craig Bertha, Ph.D., Product Quality Reviewer, DNDQA III
Suresh Doddapaneni, Ph.D., Deputy Director, Division of Clinical Pharmacology II (DCPII)
Sheetal Agarwal, Ph.D., Clinical Pharmacology Reviewer, DCPII
Joan Buenconsejo, Ph.D., Biometrics Team Leader, Division of Biostatistics II
Robert Abugov, Ph.D., Biostatistics Reviewer, Division of Biostatistics II
Miya Paterniti, M.D., Clinical Reviewer, DPARP
Erica Torjusen, M.D., Clinical Reviewer, DPARP

SPONSOR ATTENDEES:

Michael Golden, Vice President, Regulatory Affairs and Quality
Tracy Fischer, Pharm.D., Senior Director, Regulatory Affairs

Shannon Strom, Ph.D., Associate Director, Regulatory Affairs
Vidya Joshi, Ph.D., Associate Director, Regulatory Affairs
Colin Reisner, M.D., Chief Medical Officer and Executive Vice President of Clinical Dvm
Rob Schultz, Senior Director, Product Development and Product Leadership
Patrick Darken, Ph.D., Statistical Consultant
Brian Noga, Director, Product Development
Thomas Koestler, Ph.D., Pearl Therapeutics Board Member
Chad Orevillo, MPH, Vice President, Head of Medical Communications

BACKGROUND:

Pearl Therapeutics is developing GFF inhalation aerosol for long-term, twice daily maintenance treatment (b) (4) with COPD, including chronic bronchitis and emphysema. (b) (4) NDA (b) (4) planned via the 505(b)(2) pathway relying on the Agency's previous findings of safety with the reference listed drugs Foradil Aerolizer, Robinul, and Robinul Forte, and Robinul Injection. Pearl plans to file the NDA for the combination product GFF MDI (b) (4)

The EOP2 meeting request was submitted August 3, 2012, with their Annual Report for this IND. The briefing package was received November 20, 2012.

After review of the briefing package, the Division provided meeting preliminary comments to the sponsor's questions via an emailed letter on December 20, 2012.

On December 20, 2012, Pearl emailed that they would like further discussions on Clinical Questions 2a, 2b, 3, 4a, 4b, 6, 7, and 9a, as well as CMC Question 6.

The content of the letter is printed below, with the sponsor's questions from the briefing package in *italics* and the Division's comments (Meeting preliminary comments) in normal font. Summary of meeting discussions (if any) are found in **bold normal font** following the specific area of discussion.

QUESTIONS AND PRELIMINARY RESPONSES

CLINICAL, STATISTICAL, AND REGULATORY QUESTIONS

Question 1:

In the Type C Meeting Minutes for GFF MDI dated 19 April 2012, the Agency agreed with the selection of 9.6 µg of formoterol fumarate to include in FF MDI and GFF MDI for the Phase III clinical studies. As such, this question focuses on the dose selection of glycopyrrolate to include in GP MDI and GFF MDI for the Phase III clinical studies.

a. Does the Agency concur with the selection of 18 µg of glycopyrrolate as the dose for GP MDI for the Phase III clinical studies based on the results of a recently completed study (Studies PT001003), the previously completed studies and the integrated analyses of Phase II studies of 1 week in duration or longer?

FDA Response:

Based on the information you have provided, a dose of 18 mcg of glycopyrrolate seems reasonable to take forward into Phase 3. If additional safety signals are observed during your development program, revisiting this dose may be appropriate.

b. Does the Agency concur with the selection of 18 µg of glycopyrrolate as the dose for GFF MDI for the Phase III clinical studies based on the results of recently completed studies (Studies PT001003 and PT003005), the previously completed studies and the integrated analyses of Phase II studies of 1 week in duration or longer?

FDA Response:

We agree. See response to question 1a.

Question 2

a. Does the Agency concur with the designs of the proposed Phase III pivotal clinical studies (Study PT003006 and Study PT003007) and the long-term safety extension study (Study PT003008) to support NDA approvals for GFF MDI (b) (4) *?*

FDA Response:

The general design of your proposed pivotal trials is reasonable. (b) (4)

(b) (4)

Discussion:

(b) (4)

b. Does the Agency agree with the proposed primary and secondary endpoints for the Phase III pivotal studies in order to demonstrate evidence of efficacy for GFF MDI, GP MDI, and FF MDI?

FDA Response:
Use of different endpoints to assess the contribution of each monoproduct in a combination product is unusual, especially when the monocomponents share a mechanism of action. As both GP and FF are bronchodilators, we recommend using a single primary endpoint such as trough FEV1 to compare GFF to its monocomponents.

Discussion:
Pearl stated that each monocomponent showed benefit over placebo. They have also looked at trough FEV1 as a key secondary endpoint and confirmed 12-hour duration of effect with FF showing greater effect in first 6 hours and GP contributing more in the second half of the 12-hours.

FDA provided further explanation of their response above. The FDA stated that a combination product must demonstrate an added benefit over its monocomponents. This added benefit must be clinically relevant and meaningful to patients and provide justification as to why a patient would take the combination. Demonstrating that FF contributes more to the treatment effect for hours 0-6 and GP to hours 6-12 does not constitute a clinically meaningful benefit to patients of the combination over its components.

The FDA used a hypothetical example to illustrate this point. If a company were developing a hypothetical short acting beta-agonist/long-acting beta-agonist (SABA/LABA) combination product, it would be possible to use FEV1 shortly after administration to demonstrate SABA's contribution and trough FEV1 to demonstrate LABA's contribution to the combination product. However, this would clearly not represent a clinically meaningful added benefit to the patient and would not justify use of the hypothetical combination product. Of note, this hypothetical example is not a rationale combination and would not be an appropriate product for development.

While the primary endpoint chosen to demonstrate a clinically relevant added benefit of the combination over its components does not have to be trough FEV1, it should be the same endpoint for both components as both are bronchodilators. Use of two different endpoints to show contribution of components in a combination

product is generally appropriate only for monocomponents with two different mechanisms of action.

Question 3

Does the Agency agree with the approach to controlling Type 1 error in the Phase III pivotal clinical studies?

FDA Response:

We do not agree with your proposa (b) (4) Provide a clear plan to control Type 1 error across the proposed mono- and combination- therapies.

In addition, based on your protocol synopsis, you propose to apply mixed models repeated measures to evaluate treatment effects. In general this approach is reasonable. However, we are concerned about the suitability of this approach for data with treatment-related dropouts. Your protocol should carefully examine potential mechanisms which may cause data to be missing, and then detail how your proposed analyses and imputation methods may affect the estimand. In addition, reasons for discontinuation of treatment or withdrawal from the study should be recorded, avoiding less informative terms such as 'lost to follow-up,' 'patient/investigator decision,' 'withdraw consent,' in favor of categories relevant to safety or effectiveness, such as 'treatment ineffective' or 'adverse reaction.'

We refer you to "The prevention and treatment of missing data in clinical trials" by the National Research Council.

Discussion:

Pearl stated that they plan to address the missing data problem in their protocol and to capture the reasons for discontinuation in the CRF, e.g., adverse events or lack of efficacy.

FDA replied that the sponsor must carefully examine potential mechanisms which may cause data to be missing and to define what kind of an effect they are trying to estimate. (b) (4)

(b) (4)

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FDA responded that the Agency's concern was related to tachyphylaxis. (b) (4)

(b) (4)

The FDA also suggested that the

sponsor submit the SAP earlier, preferably before the trial is complete to allow for FDA review.

Question 4

(b) (4)

a. Does the Agency agree that spirometry curves and PK are not required to be evaluated in a subset of patients in the pivotal Phase III studies (Study PT003006 and Study PT003007)?

b. Does the Agency agree that the proposed study is adequate to support the inclusion of (b) (4) *-hour spirometry curves in the clinical trials section of the label?*

FDA Response to 4a and 4b:
From a PK perspective, this study provides systemic exposures of GP and FF from the respective single-ingredient products relative to the combination GFF product. If this formulation interaction data is available from other studies in humans, then you do not need to measure PK in this study. One use of collecting PK samples in Phase 3 studies is to evaluate effect of co-variates such as effect of age, gender etc., on systemic exposure of drug. Whether you choose to do this in your Phase 3 studies is at your discretion.

As your product is being dosed twice daily, (b) (4) 12 hour curves are sufficient. Replication is necessary for inclusion of spirometry curves in the product label. To fulfill this requirement, we recommend that you conduct 12 hour serial spirometry in at least a subset of patients in trials PT003006/3007. The FEV1 response over the entire dosing interval should be evaluated in the pivotal trials in order to ensure accurate labeling of drug product. (b) (4)

Discussion:
Pearl noted that they plan to evaluate PK and serial spirometry at week 1 and week 12.

FDA responded that Pearl's proposal was reasonable.

Question 5
Does the Agency agree with plans to allow patients who participated in the Phase IIb clinical studies to also participate in the Phase III clinical studies?

FDA Response:
While inclusion of patients in more than one study is not prohibited, this approach is generally not recommended. Phase 3 studies should provide independent confirmation of results from earlier studies during drug development. Inclusion of patients in more than one study may introduce selection bias which would affect both safety and efficacy

analyses. Patients who participated in phase 2b trials and agree to participate in Phase 3trials likely tolerated study drug well. These patients may have fewer AEs and safety related issues in the Phase 3 trials. While these patients would be re-randomized in Phase 3, AEs/safety signals may be under represented compared to a naïve population. As such, the safety data from these patients may not be generalizable to the COPD population as a whole. Additionally, this approach may select for patients who have obtained clinical benefit from study drug, confounding analysis of efficacy data.

Question 6

Does the Agency agree with the proposed integration plan and the sub-group analyses for the integrated summary of efficacy (ISE)?

FDA Response:

Discussion of the ISE is premature at this time. We recommend that you request a pre-NDA meeting at an appropriate time in your development program.

Question 7

Does the Agency agree with the proposed integration plan and the sub-group analyses for the integrated summary of safety (ISS)?

FDA Response:

Discussion of the ISS is premature at this time. We recommend that you request a pre-NDA meeting at an appropriate time in your development program.

Discussion:

Regarding Questions 6 & 7 (b) (4) **would like to get early thoughts regarding integration and analysis of the safety data in the pivotal trials. They would like to get input prior to the pre-NDA meeting given the lead time required to analyze the data.**

FDA stated that they do not see major concerns at this time and reiterated that it is too early to discuss the ISS. This would be more appropriate to address at the pre-NDA meeting.

Question 8

In accordance with the Draft Guidance for Industry: Applications Covered by Section 505(b)(2), October 1999, does the Agency concur that:

a. An adequate bridge has been established between FF MDI and Foradil® Aerolizer® to support a 505(b)(2) NDA for GFF MDI (b) (4) *?*

FDA Response:

We agree that you have established a PK bridge for FF in your test product to an approved reference product.

b. The large exposure margins between GP MDI and Robinul® tablets, Robinul® Forte, and Robinul® Injection provide an adequate bridge such that no clinical study is necessary to support a 505(b)(2) NDA for GFF MDI [redacted]?

FDA Response:
We agree that a relative bioavailability assessment for GP in your test product [redacted] is not needed.

Note that while there may be large margins for systemic exposure, [redacted] GFF are [redacted] locally acting drugs, clinical studies will still be necessary to assess for local safety and efficacy.

Question 9

a. Does the Agency concur with the design of the proposed study to assess the accuracy, reliability and functionality of the [redacted] dose indicator with GFF MDI?

FDA Response:
We note that the study will conclude that the dose indicator and the diary counts will be considered to be in agreement if they are within 20% of each other. We consider the level of variability to be too high and recommend that you improve the criterion for the proposed agreement between dose indicator and diary counts.

You will need to demonstrate with data that with the proposed level of counter accuracy and with consideration of overfill and manufacturing variability, the patients will be able to obtain the full number of actuations labeled to be available.

Discussion:
Pearl noted that the device has a dose indicator, not a counter. There is up to [redacted] and limited resolution. The design of the dose indicator does not allow for more resolution. At the end of the dosing period, there will be a minimum of 20 puffs left. There is less risk of under counting; thus the safety risk of no-efficacy is low.

FDA accepted the sponsor's clarification and stated that they now do not have any objections to the proposed study design.

b. [redacted]

FDA Response:
[redacted]

Question 10

a. For the Phase II studies, Clinical Data Interchange Standards Consortium (CDISC) dataset, variable and label naming conventions were utilized; however, additional variables or datasets with combined Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) variables were created where it was deemed more efficient. There are currently no plans to

modify these datasets further for submission purposes. Does the Agency agree with this approach?

FDA Response:
We agree with your proposal to include datasets which are not 100% CDISC compliant, providing you carefully document the calculation, format, and label of each variable.

b. The Sponsor plans to collect and analyze the Phase III study data using the most current CDISC standards at the time of development. Can the Agency comment on the design and acceptability of the submitted examples of the CDISC compliant electronic case report form (eCRF), SDTM and ADaM dataset specifications for one of the proposed Phase III studies?

FDA Response:
While we agree with your CDISC compliant electronic case report forms, SDTM, and ADAM datasets, also ensure that you provide programs or libraries containing formats and labels for each SDTM and ADAM dataset, programs used to construct ADAM datasets from SDTM datasets (if available), and analysis programs applied to ADAM datasets used to generate results.

Question 11
Can the Agency provide guidance on the following aspects of the GFF MDI target product profile (TPP)?
a. Does the Agency agree with the overall approach to the GFF MDI label to use primary information provided by the GFF MDI development program, supplemented with information from the 505(b)(2) reference listed products and class labeling statements from other COPD treatments, as appropriate?
b. Overall, does the Agency agree that the proposed primary and secondary endpoints and planned comparisons from Studies PT003006 and PT003007, if positive, will provide sufficient evidence to support the proposed indication statement and inclusion in the clinical trials section of the label?

(b) (4)

FDA Response to Question 11 (a,b,c,d):
While specific labeling is a review issue, we have the following general comments on your proposed TPP for your consideration.

- Your proposed labeling strategy is generally reasonable.
- We recommend use of a single primary endpoint (e.g. trough FEV1) to support the bronchodilator claim (see response to question 2).

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

Question 12

Does the Agency agree with the following proposal for IND safety reporting of serious unexpected suspected adverse reactions during the Phase III clinical studies?

a (b) (4)

FDA Response:
We do not agree. Continue to submit IND safety reports as per 21 CFR 312.32 to IND 107739 (b) (4)

b. The GFF MDI Investigator's Brochure (IB) will be the basis for determining expectedness for IND safety reporting purposes for all suspected adverse reactions in the Phase III program (b) (4)

FDA Response:
This is reasonable.

c. IND safety reports will not be submitted for any serious unexpected suspected adverse reaction for the open-label Spiriva treatment arm.

FDA Response:
No, we do not. Serious unexpected suspected adverse reactions for the open-label Spiriva treatment arms should be submitted to the IND.

CHEMISTRY, MANUFACTURING AND CONTROLS (CMC)

Question 1

Does the Agency agree that the evidence provided in support of a supplier change for glycopyrrolate is sufficient for the proposed Phase III trials?

FDA Response:
Yes, we agree.

Question 2

Does the Agency agree that the evidence provided in support of a micronization process change for glycopyrrolate is sufficient to support use of micronized (b) (4) glycopyrrolate in Phase III trials?

FDA Response:
Yes, we agree.

Question 3

Does the Agency agree with the proposed design of the NDA stability protocol?

FDA Response:
In general the stability program proposed appears comprehensive and in line with Agency recommendations, (b) (4) .

Question 4

Pearl plans to conduct full leachables and extractables testing for three unique lots of GFF MDI and leverage the data from the GFF MDI program (b) (4) registration?

FDA Response:
Your proposed approach for leachable (b) (4)

Question 5

Does the Agency concur with the proposed Phase III specifications for the following?
a) Drug product
b) Drug substances
c) Excipients - porous particles and its components, and propellant
d) (b) (4)
e) CCS components and packaging materials

FDA Response:
In general, the specifications proposed for Phase 3 for the drug product, drug substances, excipients (porous particles and its components, and propellant), (b) (4) , and CCS components and packaging materials are acceptable from a safety perspective. However, final agreement regarding these specifications, as part of your quality control strategy for the drug product, will be made subsequent to our complete evaluation of the associated data and justifications provided in your NDA. Nevertheless, we have some general comments for you to consider based on our cursory review of the summary information provided (these may not necessarily be all inclusive).

The specifications for the drug product and the various drug product components should be comprehensive and include all pertinent tests performed both by the suppliers and by Pearl, i.e., the eventual NDA should include single specifications for the drug product and each component.

A "visual review" of the supplier's certificate of analysis does not fulfill the GMP requirement to validate the supplier's results at appropriate intervals.

Glycopyrrolate (GP) Specification – Provide justification, supported with data where needed, in the NDA for the absence of specific recommended tests currently not included, e.g., (b) (4) surface area, water content, melting range, heavy metals.

Formoterol Fumarate (FF) Specification – Provide justification, supported by data where needed, in the NDA for the absence of specific recommended tests currently not included, e.g., surface area, melting range.

(b) (4)

Alternatively, add the indicated test attributes to the various specifications.

Question 6
Does the Agency agree that an appropriate CMC link has been established with respect to the changes made to the product between Phase IIb and Phase III?

FDA Response:
The *in vitro* performance data presented for the monotherapy and combination drug products of the 2.3/4.8 mcg GP/FF strengths, both before and after the product changes, are considered to be comparable. However, it is not necessarily the case that the higher strength combination and monotherapy products would behave in the same way. Thus, once you manufacture the 9.0/4.8 mcg strength and comparators with the product changes, provide the analogous data to the IND. Proceeding with large Phase 3clinical studies, prior to demonstrating to the Division the *in vitro* performance comparability between the combination and the two monotherapy drug products for the final chosen strengths, is not recommended.

Discussion:
Pearl stated that they would submit the comparative data 30 days prior to starting the clinical study.

FDA responded that should provide sufficient time to review the data.

Question 7
Does the Agency agree that the approach as described below for making the changeover to the (b) (4) *subsequent to Phase III clinical trials, but prior to NDA submission is acceptable?*

FDA Response:
Yes, we agree with the approach proposed.

Question 8

In addition to the 120 actuation product (commercial pack), (b) (4)

(b) (4)

FDA Response:

(b) (4)

b. (b) (4)

FDA Response:
See response to 8a above.

Additional CMC-Related Comment
As you proceed with your development, for the final to-be-marketed drug product, perform characterization studies as outlined in the Agency draft CMC guidance for inhalation aerosol drug products at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070573.pdf.

In order to assess the robustness of your device under patient use and misuse scenarios, we recommend that you perform a robustness evaluation of your drug product by evaluating the performance (delivered dose and aerodynamic particle size distribution (APSD)) for about 100 used (at least about seventy five percent of labeled doses used) and returned devices from the Phase 3trials. In addition, all devices that are deemed malfunctioning or broken should be assessed and evaluated for performance to the extent possible.

Additional Comments regarding 505(b)(2) drug development
We note you are planning to use Robinul, Robinul Forte and Foradil Aerolizer (NDAs 20831,

21279, 17558, and 12827) as the reference listed drugs. Refer to Type C meeting Written Responses dated April 19, 2012, for additional information.

PREA PEDIATRIC STUDY PLAN

Please be advised that you must submit a Pediatric Study Plan within 60 days of your scheduled end-of-Phase 2 meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. For additional guidance on submission of the PSP you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

ISSUES REQUIRING FURTHER DISCUSSION:

There were no issues requiring further discussion.

ATTACHMENTS AND HANDOUTS:

There were no attachments or handouts for the meeting minutes.

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

/s/

CHRISTINE H CHUNG
01/17/2013