

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208780Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 208780

SUPPL #

HFD # 570

Trade Name Esbriet Film-coated Tablets

Generic Name pirfenidone film-coated tablets

Applicant Name Genentech, Inc.

Approval Date, If Known January 11, 2017

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(1)

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.

Applicant submitted data from a single pharmacokinetic study (GP29830) assessing the bioequivalence (BE) of pirfenidone tablets and the reference listed drug, pirfenidone capsules.

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?

7-years, this was granted under NDA 22535 for pirfenidone capsules. Pirfenidone capsules received FDA approval on October 15, 2014, under NDA 22535. Pirfenidone received orphan drug designation on March 5, 2004.

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# 22535 Pirfenidone Capsules

NDA#

NDA#

2. Combination product.

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

YES NO

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

YES NO

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

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

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

YES NO

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

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

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

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

Investigation #1 YES NO

Investigation #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: Jessica Lee, PharmD
Title: Regulatory Project Manager
Date:

Name of Division Director signing form: Badrul A. Chowdhury, MD, PhD
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/

JESSICA K LEE
01/11/2017

BADRUL A CHOWDHURY
01/11/2017

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 208780 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Esbriet Established/Proper Name: pirfenidone Dosage Form: Film-coated Tablets		Applicant: Genentech, Inc. Agent for Applicant (if applicable):
RPM: Jessica Lee		Division: DPARP
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p>For ALL 505(b)(2) applications, two months prior to EVERY action:</p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>) Date of check:</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>1/27/17</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> 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)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

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

NDAs: Subpart H

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

Subpart I

- Approval based on animal studies

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

BLAs: Subpart E

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

Subpart H

- Approval based on animal studies

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

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> 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	<input checked="" type="checkbox"/> No <input type="checkbox"/> 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.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s) Approval 1/11/17
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
<ul style="list-style-type: none"> • Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
<ul style="list-style-type: none"> • Most-recent draft labeling 	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
<ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i> • Review(s) <i>(indicate date(s))</i> 	9/14/16 (acceptable) 9/14/16; 8/10/16
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input type="checkbox"/> None 6/7/16 DMEPA: <input type="checkbox"/> None 9/20/16 DMPP/PLT (DRISK): <input type="checkbox"/> None 11/22/16 OPDP: <input type="checkbox"/> None 11/23/16 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input type="checkbox"/> None Other: <input type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i>	6/7/16
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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

<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director’s Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>This product has orphan designation.</u> 	
❖ Breakthrough Therapy Designation	<input type="checkbox"/> N/A
<ul style="list-style-type: none"> Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	
<ul style="list-style-type: none"> CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	
<ul style="list-style-type: none"> CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>)	12/13/16; 12/1/16; 9/19/2016; 9/12/2016; 8/29/16; 8/23/16; 8/16/16; 7/20/16; 7/8/16; 7/5/16; 7/1/16; 6/8/16; 4/11/16
❖ 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	
<ul style="list-style-type: none"> If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 2/1/16 (meeting cancelled, prelim comments enclosed)
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg
<ul style="list-style-type: none"> Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A
<ul style="list-style-type: none"> Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A
<ul style="list-style-type: none"> Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	CMC WRO-5/27/15
❖ Advisory Committee Meeting(s) <ul style="list-style-type: none"> Date(s) of Meeting(s) 	<input type="checkbox"/> No AC meeting
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 1/11/17
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 12/15/16
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None

Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> No separate review
• Clinical review(s) (indicate date for each review)	11/22/16; 5/13/16
• Social scientist review(s) (if OTC drug) (indicate date for each review)	<input type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (indicate date of review/memo)	
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review) ⁵	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> • 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) 	<input type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)	<input checked="" type="checkbox"/> None requested
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None 6/10/16
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> No separate review
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 11/23/16; 5/18/16
❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	<input type="checkbox"/> None requested 9/26/16; 6/26/16

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

Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 10/17/16; 5/13/16
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 11/30/16; 5/6/16; 3/31/16
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	<input type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	12/1/16
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input type="checkbox"/> Facilities inspections (<i>action must be taken prior to the re-evaluation date</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	<input checked="" type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

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

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

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

/s/

JESSICA K LEE
01/12/2017



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

DATE: December 13, 2016

To: Isa Samuels Regulatory Program Director	From: Jessica Lee, PharmD Senior Regulatory Project Manager
Company: Genentech	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number:	Fax number: 301-796-9728
Phone number: 650-255-5911	Phone number: 301-796-3769

Subject: NDA 208780, Pirfenidone, Labeling Information Request #2

Total no. of pages including cover:

Comments: Please confirm receipt.

Document to be mailed: YES xNO

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Dear Ms. Samuels,

Your submission dated, March 29, 2016, to NDA 208780, is currently under review. Please refer to the submissions dated December 8, 2016. We have the following comment to all Carton & Container labels. Our revisions to your proposed Patient Information (PPI) are attached. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as we continue to review the label.

Carton & Container Labels:

The (b) (4) colors used to for the 267 mg and 801 mg strengths, respectively, appear similar. Therefore, we recommend changing the color of 801 mg strength to provide more adequate differentiation between the two strengths.

Provide a response by December 15, 2016. The information can be sent by electronic mail to Jessica.Lee@fda.hhs.gov, followed by an official submission to the NDA. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

Drafted by: JLee 12/12/16
MMistry 12/9/16
CMcGuire 12/13/16

Initialed by: ADurmowicz 12/13/16
LJafari 12/13/16

Finalized by: JLee 12/13/16

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

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/s/

JESSICA K LEE
12/13/2016



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

DATE: December 1, 2016

To: Isa Samuels Regulatory Program Director	From: Jessica Lee, PharmD Senior Regulatory Project Manager
Company: Genentech	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number:	Fax number: 301-796-9728
Phone number: 650-255-5911	Phone number: 301-796-3769

Subject: NDA 208780, Pirfenidone, Labeling Information Request

Total no. of pages including cover:

Comments: Please confirm receipt.

Document to be mailed: YES xNO

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Dear Ms. Samuels,

Your submission dated, March 29, 2016, to NDA 208780, is currently under review. We have the following changes to all Carton & Container labels. Our revisions to your proposed package insert (PI) and Patient Information (PPI) are attached. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as we continue to review the label.

Changes to all Carton & Container Labels

- 1) The established name lacks prominence commensurate with the proprietary name. Increase the prominence (use bold font) of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
- 2) There is inadequate differentiation between the 267 mg and 801 mg strengths. We recommend the revision of the 801 mg carton and container labels with the use of different colors, boxing, or some other means to provide adequate differentiation between the strengths.

Provide a response by December 8, 2016. The information can be sent by electronic mail to Jessica.Lee@fda.hhs.gov, followed by an official submission to the NDA. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

Drafted by: CMcGuire 11/29/16
JLee 11/29/16

Initialed by: LJafari 11/29/16
ADurmowicz 11/29/16
AMarathe 12/1/16

Finalized by: JLee 12/1/16

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

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/s/

JESSICA K LEE
12/01/2016

From: [Isa Samuels](#)
To: [Aisida, Bamidele \(Florence\)](#)
Subject: Re: INFORMATION REQUEST NDA 208780
Date: Monday, September 19, 2016 8:29:36 PM

Dear Florence,

I confirm receipt of your email. We will respond as requested.

Thank you,
Isa

Isa Samuels | Regulatory Program Management, Product Development | Genentech, Inc. | Mail Stop 35-N5-7 | 1 DNA Way, South San Francisco, CA 94080, USA | phone: +1-650-255-5911.

This email and any and all attachments contain information that is confidential and may not be disclosed without prior written consent from Genentech/Roche.

On Mon, Sep 19, 2016 at 12:58 PM, Aisida, Bamidele (Florence) <Bamidele.Aisida@fda.hhs.gov> wrote:

Hello Ms. Samuels,

I have received the following information request from our CMC review team. Please respond to the following with a submission to your NDA by Monday, October 3, 2016:

1. Please specify in the batch formula the quantities of all ingredients used in the manufacturing process, including th (b) (4). The quantity should be specified and justified by your developmental and manufacturing data.
2. The agency acknowledges that your batch formulas list the quantity of each ingredient for the overall batch size. (b) (4)
3. Please define (b) (4) and the procedure to measure and/or calculate it
4. Please add (b) (4)—in the equipment list.
5. Please add the (b) (4) in the Description of Manufacturing Process.

6. Since you have not provided any blend uniformity data in the application, please commit to conducting blend uniformity test at least for the first three commercial batches of final blend.

Additional Comment: The term drug “overage” applies specifically to the drug substance (see ICH Q8). Please use a term other than “overage” to describe the (b) (4) in the batch formula table and throughout the NDA.

Please confirm receipt of this email.

Thanks,

Florence Aisida, Pharm.D,BCPS

Regulatory Business Process Manager

HHS | FDA | CDER

Office of Pharmaceutical Quality

Office of Program and Regulatory Operations

Bamidele.aisida@fda.hhs.gov | [240.402.2691](tel:240.402.2691)

From: [Aisida Bamidele \(Florence\)](#)
To: "Isa Samuels"
Cc: [Lee Jessica K \(ODEII/DPARP\)](#); [Kinsley Steven](#)
Subject: INFORMATION REQUEST NDA 208780
Date: Monday, September 12, 2016 12:24:12 PM

Hello Mr. Samuels,

I have received the following information request from our CMC review team. Please respond to the following with a submission to your NDA by Monday, October 3, 2016:

Please refer to CTD Section 1.12.14, Environmental Analysis, in which you provide an environmental assessment (EA), dated March 31, 2016. The EA concludes that use of the drug is not likely to cause any significant adverse effects on the environment. As noted in Appendix D (Clinical Investigator's Brochure) and references, however, pirfenidone may cause sex hormone imbalance through release of hypothalamic dopamine, which in turn appears to reduce prolactin levels and alter the estradiol/progesterone ratio. This raises concern for hormonal effects in the environment, which is the subject of FDA's recently finalized environmental guidance related to drugs with potential estrogenic, androgenic, or thyroid activity (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444658.pdf>). While the lowest assessment factor (AF) of >8,000 noted in the EA is still substantial, this is based on OECD 210, fish early life stage test, which does not address several of the potential hormonal effects noted in the new FDA guidance. FDA subsequently conducted a plasma fish analysis, as shown in the table below, which resulted in an AF (ER) of >14,000, also clearly substantial. Note, however, that this model used the EA's log P (log D) of 0.9, while predicted log Ps were found ranging from 1.69

(b) (4)

to 2.14

(b) (4)

. This latter log P would result in an AF (ER) closer to 1,000, the limit recommended by Huggett et al. (2003). Therefore, please confirm the source of the log P (log D) of 0.9. In addition, please provide a literature search and discussion of any additional information that could elucidate the potential for environmental effects, such as from adverse outcome pathway/mechanistic data, other dopamine agonists that could be used for "read across" and cumulative risk purposes, and data on metabolism, fate, and transport that can be used to refine environmental concentration estimates and risk characterization.

Fish Plasma Model (Huggett et al., 2003)				Comments
Input Data				
API	Pirfenidone			
NDA	208780			
Date Evaluated	9/7/2016			
Therapeutic concentration	14.7	ug/mL or mg/L		NDA 208870- pg. 65 EA
Log D at pH 7.0	0.9			NDA 208870- pg. 6 EA
MEEC	1.4	ug/L	ppb	NDA 208870- pg. 32 EA
Calculated Values for D_{lip} and $P_{b/w}$				
Log D_{lip} (Liposome:water distribution coefficient)	1.0			QSAR of Tanoue et al., 2015
log $P_{b/w}$	-0.1			QSAR of Scott et al., 2016
$P_{b/w}$ (Water to plasma coefficient for fish)	0.7			
Effect Ratio				
ER	14126			< 1,000 evaluate the need for further fish chronic exposure studies

Please confirm receipt of this email.

Florence Aisida, Pharm.D,BCPS
RBPM, Office of Program and Regulatory Operations
Office of Pharmaceutical Quality/CDER/FDA.
[\(240\) 402-2691](tel:(240)402-2691) | Bamidele.aisida@fda.hhs.gov



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

DATE: August 29, 2016

To: Isa Samuels Regulatory Program Director	From: Jessica Lee, PharmD Senior Regulatory Project Manager
Company: Genentech	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number:	Fax number: 301-796-9728
Phone number: 650-255-5911	Phone number: 301-796-3769

Subject: [NDA 208780 Information Request](#)

Total no. of pages including cover:

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Dear Ms. Samuels,

Your submission dated, March 29, 2016, to NDA 208780, is currently under review. We have the following request for information:

Reference is made to your Bioanalytical report for Study GP29830. Provide the dilution factor used for all study samples for Study GP29830, or refer us to the location of this information in your submission.

Provide a response by September 6, 2016. The information can be sent by electronic mail to Jessica.Lee@fda.hhs.gov, followed by an official submission to the NDA. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

Drafted by: BSaluja 8/26/16
JLee 8/29/16

Initialed by: LJafari 8/29/16
AMarathe 8/29/16

Finalized by: JLee 8/29/16

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/s/

JESSICA K LEE
08/29/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 08/23/2016 10:32:53 AM
To: samuels.isa@gene.com
CC: Jessica.Lee@fda.hhs.gov
BCC: Bamidele.aisida@fda.hhs.gov
Subject: INFORMATION REQUEST NDA 208780

Hello Mr. Samuels,

I have received the following information request from our CMC review team. Please respond to the following with a submission to your NDA by Friday, August 26, 2016:

We noticed that the file for 3.2, Section S.3.1., 'elucidation-of-structure.pdf' appears to be missing or corrupted in the eCTD.
Could you please resend the file?

Please confirm receipt of this email.

Florence Aisida, Pharm.D, BCPS
RBPM, Office of Program and Regulatory Operations
Office of Pharmaceutical Quality/CDER/FDA.
(240) 402-2691 | Bamidele.aisida@fda.hhs.gov



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

DATE: August 16, 2016

To: Isa Samuels Regulatory Program Director	From: Jessica Lee, PharmD Senior Regulatory Project Manager
Company: Genentech	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number:	Fax number: 301-796-9728
Phone number: 650-255-5911	Phone number: 301-796-3769

Subject: [NDA 208780 Pirfenidone Information Request](#)

Total no. of pages including cover:

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Document to be mailed: YES xNO

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Dear Ms. Samuels,

Your submission dated March 29, 2016, to NDA 208780, is currently under review. We have the following requests for information:

1. The submitted draft labeling describes (b) (4) Section 3 Dosage Forms and Strengths (b) (4). However, Section 16 How Supplied/Storage and Handling does not include a complete description (b) (4) (b) (4) and the Patient Information “How should I take Esbriet” instructions do not include (b) (4). Please clarify.

Provide a response by August 23, 2016. The information can be sent by electronic mail to Jessica.Lee@fda.hhs.gov, followed by an official submission to the NDA. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

Drafted by: CMcGuire 8/10/16
JLee 8/16/16

Initialed by: ADurmowicz 8/10/16
LJafari 8/16/16

Finalized by: JLee 8/16/16

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/s/

JESSICA K LEE
08/16/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208780

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990

ATTENTION: Isa Samuels
Regulatory Program Director, Product Development

Dear Mr. Samuels:

Please refer to your New Drug Application (NDA) dated and received March 29, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pirfenidone Film-Coated Tablets, 267 mg, 534 mg and 801 mg.

We also refer to your correspondence, dated and received May 26, 2016, requesting review of your proposed proprietary name, Esbriet.

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

If any of the proposed product characteristics as stated in your above 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 Michael Sinks, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-2684. For any other information regarding this application, contact Jessica Lee, Regulatory Project Manager in the Office of New Drugs, at (301) 796-3769.

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/

LUBNA A MERCHANT on behalf of TODD D BRIDGES
08/15/2016

From: [Aisida, Bamidele \(Florence\)](#)
To: ["samuels.isa@gene.com"](mailto:samuels.isa@gene.com)
Cc: [Lee, Jessica K \(ODEII/DPARP\)](#)
Subject: NDA 208780 IR
Date: Wednesday, July 20, 2016 12:47:50 PM

Hello Mr. Samuels,

I have received the following information requests from our CMC review team. Please respond to the following with a submission to your NDA by Friday, July 29, 2016:

We have noted in the stability data submitted to the NDA, that assay content is on the low end of the proposed specification and appear to increase over time in a few cases. Please explain.

Please confirm receipt of this IR.

Thanks,

Florence Aisida, Pharm.D,BCPS

Regulatory Business Process Manager
HHS | FDA | CDER
Office of Pharmaceutical Quality
Office of Program and Regulatory Operations
Bamidele.aisida@fda.hhs.gov | 240.402.2691

Sinks, Michael

From: Sinks, Michael
Sent: Friday, July 01, 2016 11:33 AM
To: 'samuelsi@gene.com'
Cc: Rashid, Nichelle E
Subject: Esbriet (Pirfenidone) NDA 208780 Film-Coated Tablets: Immediate Response

Follow Up Flag: Follow up
Due By: Tuesday, July 05, 2016 4:00 PM
Flag Status: Flagged

Good afternoon Mr. Samuels,

Please refer to your New Drug Application dated and received on March 29, 2016, for Pirfenidone (NDA 208780).

We also refer to your correspondence, dated and received May 26, 2016, for your Request for Proprietary Name Review of Esbriet.

The carton and container labeling for Esbriet (pirfenidone) [REDACTED] (b) (4) was not included in your March 29, 2016 submission. Please submit the proposed carton and container labeling for the 534 mg strength by **July 8, 2016**.

Warm regards,

Michael Sinks, Pharm. D.
FDA Project Manager
Office of Surveillance and Epidemiology
Office Phone: (240)402-2684
Work Cell: [REDACTED] (b) (6)
Email: Michael.Sinks@FDA.hhs.gov

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/s/

MICHAEL A SINKS
07/08/2016



NDA 208780

**PROPRIETARY NAME
ACKNOWLEDGEMENT**

Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990

ATTENTION: Isa Samuels
Regulatory Program Director, Product Development

Dear Mr. Samuels:

Please refer to your New Drug Application (NDA) dated and received March 29, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pirfenidone Tablets, 267 mg, 534 mg, and 801 mg.

We acknowledge receipt of your correspondence, dated and received May 26, 2016, requesting a review of your proposed proprietary name, Esbriet.

The user fee goal date is August 24, 2016.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Michael Sinks, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-2684. For any other information regarding this application, contact Jessica Lee, Regulatory Project Manager, in the Office of New Drugs at (301) 796-3769.

Sincerely,

{See appended electronic signature page}

Dr. Michael Sinks, PharmD
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

MICHAEL A SINKS
07/08/2016

From: [Aisida, Bamidele \(Florence\)](#)
To: ["samuels.isa@gene.com"](mailto:samuels.isa@gene.com)
Cc: [Lee, Jessica K \(ODEII/DPARP\)](#)
Subject: NDA 208780 IR
Date: Tuesday, July 05, 2016 2:35:36 PM

Hello Mr. Samuels,

Please confirm that you are proposing to use the drug substance sourced from both (b) (4) to support NDA 208780. If so, please update the 356h form to include the (b) (4) manufacturer as an additional drug substance manufacturing site. This also needs to be clear in S.2 section of module 3.

Please respond to the following by Wednesday, July 6, 2016 COB

Florence Aisida, Pharm.D,BCPS

Regulatory Business Process Manager
HHS | FDA | CDER
Office of Pharmaceutical Quality
Office of Program and Regulatory Operations
Bamidele.aisida@fda.hhs.gov | 240.402.2691



NDA 208780

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

Genentech, Inc.
1 DNA Way MS 35-5G
South San Francisco, CA 94080-4990

Attention: Isa Samuels
Regulatory Program Director
Product Development

Dear Ms. Samuels:

Please refer to your New Drug Application (NDA) dated March 29, 2016, received March 29, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Esbriet (pirfenidone) Film-coated Tablets.

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 January 29, 2017.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by January 1, 2017.

At this time, we are notifying you that, we have not identified any 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.

We request that you submit the following information:

1. Contact the holders of the referenced Drug Master Files (DMFs) and have them resubmit letters of authorization that provide sufficient information to allow us to locate the information referenced for your application (i.e., amendment date(s), page numbers).

PRESCRIBING INFORMATION

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

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

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

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

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 patient PI (as applicable). 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 patient PI (as applicable), and you believe the labeling is close to the final version.

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

REQUIRED PEDIATRIC ASSESSMENTS

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

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

If you have any questions, call Jessica Lee, Regulatory Project Manager, at (301) 796-3769.

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
06/08/2016



NDA 208780

NDA ACKNOWLEDGMENT

Genentech, Inc.
1 DNA Way MS 35-5G
South San Francisco, CA 94080-4990

Attention: Isa Samuels
Regulatory Program Director
Product Development

Dear Ms. Samuels:

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

Name of Drug Product: Esbriet (pirfenidone) Film-coated Tablets

Date of Application: March 29, 2016

Date of Receipt: March 29, 2016

Our Reference Number: NDA 208780

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 May 28, 2016, 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/FederalFoodDrugandCosmeticActFDCA/ct/SignificantAmendmentstotheFDCAAct/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 208780** submitted on March 29, 2016, 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) 796-3769.

Sincerely,

{See appended electronic signature page}

Jessica K. Lee, PharmD
Senior 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/

JESSICA K LEE
04/11/2016

For Internal Use Only

Meeting Request Withdrawn/Meeting Cancellation Form

Application Type/Number	PIND 67284
Meeting Type/Code	Type B/Pre-NDA
DATE Meeting Request Withdrawn by Sponsor	
DATE Meeting Cancelled by Sponsor or FDA (per communication with sponsor)	Jan 29, 2016
DATE FDA-Initiated Meeting Cancelled (per communication with sponsor)	
Scheduled Meeting Date	Feb 1, 2016
Reason for Withdrawal/Cancellation	In an electronic mail dated, January 29, 2016, Genentech proposed to cancel Feb. 1, 2016 meeting as the feedback provided in the Preliminary Comments, dated Jan. 28, 2016, was clear and further discussion was not needed. Additionally, Genentech acknowledged that the Preliminary Comments would represent the official record of the meeting.
Project Manager	Jessica Lee, PharmD

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/s/

JESSICA K LEE
02/01/2016



IND 67284

MEETING PRELIMINARY COMMENTS

Genentech, Inc.
1 DNA Way
MS# 35-5G
South San Francisco, CA 94080-4990

Attention: Isa Samuels
Regulatory Program Management

Dear Ms. Samuels:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Esbriet (pirfenidone).

We also refer to your December 4, 2015, correspondence, received December 4, 2015, requesting a meeting to discuss the proposed structural content and format of the film-coated tablet New Drug Application (NDA).

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at (301) 796-3769.

Sincerely,

{See appended electronic signature page}

Jessica K. Lee, PharmD
Senior Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II

IND 67284
Page 2

Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: February 1, 2016
Meeting Location: via Teleconference

Application Number: IND 67284
Product Name: Esbriet (pirfenidone)
Indication: Idiopathic Pulmonary Fibrosis (IPF)
Sponsor Name: Genentech, Inc.

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for February 1, 2016, 12:00pm, via teleconference between Genentech and the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP). We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

In a submission dated, December 4, 2015, Genentech requested a meeting to discuss the proposed structural content and format of the film-coated tablet New Drug Application (NDA). Additionally, in an electronic correspondence dated, December 14, 2015, between Isa Samuels of Genentech and Jessica Lee of DPARP, Genentech clarified that the meeting request was for a Pre-NDA meeting. The meeting was granted on December 16, 2015. Genentech's specific questions from the Briefing Document dated, December 4, 2015, are listed below in *italics* and FDA responses are provided in normal font.

2.0 DISCUSSION

Question 1:

The Sponsor plans not to include the following Modules in the NDA for Esbriet tablets. The tablet NDA will cross-refer to IND 67284 and NDA 22535. Does the Agency agree with the proposed plan?

- *Module 2.4 Nonclinical Overview*
- *Module 2.6 Nonclinical written and tabulated summaries*
- *Module 2.7.3 Summary of Clinical Efficacy*
- *Module 2.7.4 Summary of Clinical Safety*
- *Module 4 Nonclinical Study Reports*
- *Module 5.3.5.3 Integrated Summary of Safety and Integrated Summary of Efficacy*

FDA Response to Question 1:

We agree that nonclinical modules 2.4, 2.6, and 4 and clinical modules 2.7.3 and 2.7.4 and 5.3.5.3 can be cross referenced.

Question 2:

The Sponsor plans to submit the periodic benefit-risk evaluation report (PBRER) and periodic adverse drug experience report (PADER) to NDA 22535 according to the Agency's waiver (dated 6 July 2015) and will include safety updates obtained from Study GP29830. Does the Agency agree that a 120-day safety update report will not be necessary for the planned film-coated tablet NDA?

FDA Response to Question 2:

We do not agree; the 120-day safety update is required and should be submitted to the film coated tablet NDA. If no new data is available at the time of the 120-day safety update this should be stated in the safety update submitted to the NDA.

Question 3:

Does the Agency agree with the proposed content of the Module 5 datasets package submission, including the structure and format of the datasets for Study GP29830 as described below?

FDA Response to Question 3:

This is acceptable.

Question 4:

Does the Agency concur with the proposed structural format and key contents of the electronic common technical document (eCTD) as described in Appendix 1?

FDA Response to Question 4:

Your proposal is acceptable.

3.0

PREA REQUIREMENTS

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

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

PRESCRIBING INFORMATION

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

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

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

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

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

Office of Scientific Investigations (OSI) Requests

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

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

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

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

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

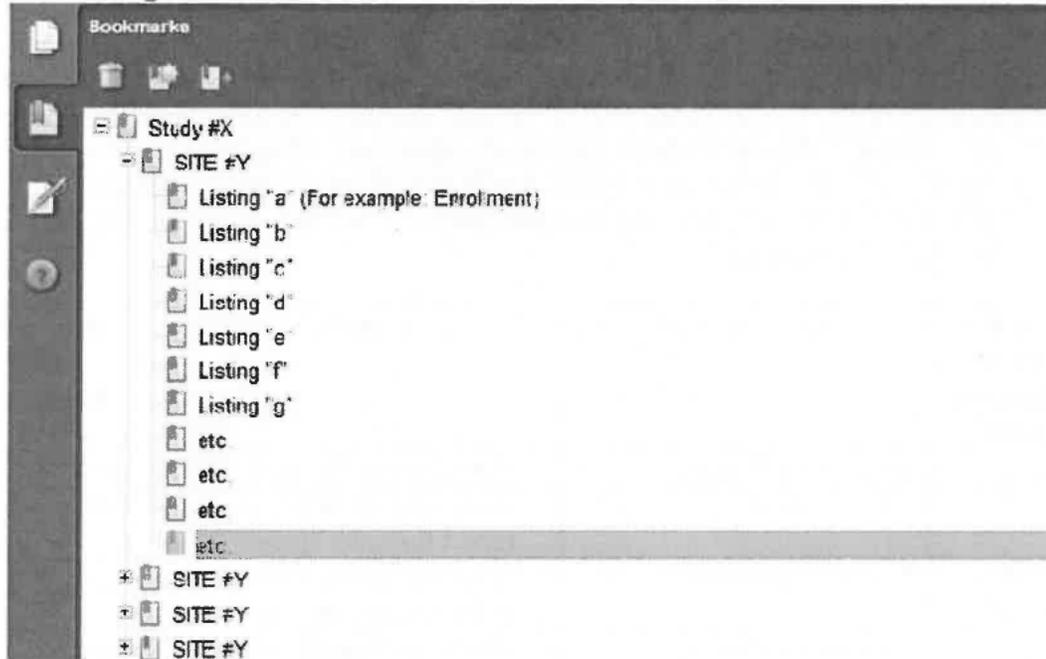
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:

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

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.

- i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

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

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

DSI Pre-NDA Request Item¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

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

```
= [m5]
  = datasets
    = bimo
      = site-level
```

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

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

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

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

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

/s/

JESSICA K LEE
01/28/2016



IND 67284

**MEETING REQUEST-
WRITTEN RESPONSES**

Genentech, Inc.
1 DNA Way, MS #242
South San Francisco, CA 94080-4990

Attention: Cindy Wu
Pharma Technical Regulatory

Dear Ms. Wu:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Esbriet (pirfenidone) Capsules.

We also refer to your submission dated March 13, 2015, containing a Type C meeting request. The purpose of the requested meeting was to discuss CMC development and clinical protocol of a bioequivalence study comparing the tablet formulation to the currently marketed capsule formulation.

Further reference is made to our Meeting Granted letter dated March 23, 2015, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your March 24, 2015 background package.

If you have any questions, call me at (301) 796-3769.

Sincerely,

{See appended electronic signature page}

Jessica K. Lee, PharmD
Senior Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:

Written Responses



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: C
Meeting Category: Guidance

Application Number: IND 67284
Product Name: Esbriet (pirfenidone) Capsules
Indication: Idiopathic Pulmonary Fibrosis
Sponsor Name: Genentech, Inc.
Regulatory Pathway: 505(b)(1)

1.0 BACKGROUND

Genentech submitted a Written Response Only Type C meeting dated, March 13, 2015, to discuss the CMC development and clinical protocol of a bioequivalence study comparing the tablet formulation to the currently marketed capsule formulation. The meeting for Written Responses was granted on March 23, 2015. Genentech's specific questions from the Briefing Document dated, March 24, 2015, are listed below in *italics* and the FDA responses are provided in normal font.

2.0 QUESTIONS AND RESPONSES

Question 1:

Does the FDA agree with the registration strategy to support two commercial Drug Substance manufacturing sites in the sNDA application for the film-coated tablets?

FDA Response to Question 1:

The FDA does not approve process validation approaches, protocols, or number of specific batches used in process validation studies. The actual protocols, acceptance criteria and study outcomes (as applicable) will be evaluated during an inspection of your manufacturing facilities. The product design and the suitability of manufacturing processes will be evaluated during the NDA review cycle. It is your company's responsibility to conduct all studies necessary to assure your commercial manufacturing process is capable of consistently delivering quality product.

The FDA requires that drug manufacturers validate their manufacturing processes [21 CFR 211.100(a) and 211.110(a)] but does not prescribe how that is to be accomplished as it will depend on multiple factors, some of which are specific to the complexity of the product and process. The process validation protocol should be built on an understanding of the process gathered from experience executing development batches (Process Validation Stage 1). Subsequent design of the facility, qualification of equipment/utilities, verification of material

sources, and operational performance qualification (Process Validation Stage 2) should be incorporated into the proposed commercial scale manufacturing process and control strategy as well as the Process Performance Qualification protocol. Likewise, knowledge obtained during transfer and scale up activities can be useful in further developing the control strategy. Successful process validation should also include a plan for continued process assessment (Stage 3) to monitor and trend quality of incoming materials or components, in-process material, and finished products.

For additional information on process validation, please refer to “Guidance for Industry, Process Validation: General Principles and Practices” posted at the following link.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf>

For further information on Agency’s drug compliance and pre-approval inspection programs please refer to the following links on FDA’s website:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm252671.htm>

Question 2:

Does the FDA agree with the proposal to submit six months of Drug Product (film-coated tablets) stability data with additional three months data (nine months in total) to be provided within two months after sNDA submission, thus supporting a shelf-life of [REDACTED] ^{(b) (4)} ?

FDA Response to Question 2:

Yes, we agree with the amount of data to be provided at the time of submission of the application. However, if these data show significant trends not evident for the approved capsule drug product, it is likely that your expiry period for the tablet products may be limited.

Question 3:

To comply with requirements set forth in 21 CFR 314.50(d)(1)(ii)(b) regarding the submission of the batch production records for the batches used to conduct the bioequivalence study and those used to conduct the primary stability study, the Sponsor intends to only include a copy of the bilingual Italian/English version of the 801 mg film-coated tablet master production record and a copy of the executed batch record (in Italian) for the actual 801 mg film-coated tablet primary sNDA stability batch, which is used to conduct the bioequivalent study.

Executed batch records of all the other primary site stability batches included in the sNDA will be available at the manufacturing site at Roche S.p.A., Segrate, Italy, and will be available upon request.

Does the FDA agree with this approach?

FDA Response to Question 3:

It is sufficient to submit the Italian master production record and an English translation of this master production record for only the 801mg strength. However, since stability data will be submitted for all three strengths of the coated tablet drug product, an executed batch record for each tablet strength should be submitted according to 21 CFR 314.50(d)(ii)(b). These executed batch records are acceptable in their original language.

Question 4:

- a) *Does the Agency agree that the proposed bioequivalence study comparing the proposed market formulation, an immediate release 801 mg pirfenidone tablet, to three 267 mg pirfenidone capsules is adequate to support the potential registration of the 801 mg tablet, as well as the two lower-dose pirfenidone tablets?*
- b) *Does the Agency agree with conducting the bioequivalence study under fed conditions?*

FDA Response to Question 4:

- a) We agree with the proposed dose and study population in the single-dose crossover BE study. However, we recommend that you assess the bioequivalence under fasting conditions, as stated in response to Question 4b. The acceptance of the data will be a review issue.

For sample size calculation, we agree that the equivalence margin of 0.8-1.25 is reasonable, and we agree on the 90% CI for the ratio of geometric means of test/reference for the PK parameters. The other aspects of sample size calculation, such as coefficient of variation, power of the study (at least 80%), assumption of the ratio of geometric means between test product and reference product, and assumption of dropout rate are at your discretion.

Regarding the waivers for the lower strengths (267 mg and 534 mg), your approach to support a biowaiver request seems reasonable (based on proposed comparative dissolution between the highest strength biobatch and the lower strengths, and dissolution in multi-pH media).

See the following comments regarding the dissolution information that should be provided in your NDA:

Dissolution Test: Include the dissolution method report supporting the selection of the proposed dissolution test. The dissolution report should include the following information:

- a. Solubility data for the drug substance covering the pH range.
- b. Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (i.e., selection of the

equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.) used to select the proposed dissolution method as the optimal test for your product. If a surfactant was used, include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete and cover at least 85% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend use of at least twelve samples per testing variable.

- c. Provide the complete dissolution profile data (individual, mean, SD, profiles) for your product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim).
- d. Data to support the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., $\pm 10\text{-}20\%$ change to the specification-ranges of these variables).
- e. Supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).

Dissolution Acceptance Criterion: For the selection of the dissolution acceptance criterion of your product, the following points should be considered:

- a. The dissolution profile data from the pivotal clinical batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criterion of your product (i.e., specification-sampling time point and specification value).
 - b. The in vitro dissolution profile should encompass the timeframe over which at least $\frac{(b)}{(4)}\%$ of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution is occurring.
 - c. For immediate release product the selection of the specification time point should be at least where $Q = \frac{(b)}{(4)}\%$ dissolution occurs.
- b) No, we do not agree. Fasting state provides more sensitive conditions in assessing formulation differences. While nausea was observed in the initial food effect study under fasting conditions, the overall available information suggests that side effect of nausea is

not severe enough to preclude the study conducted under fasting conditions. We recommend that you assess the bioequivalence under fasting conditions, and provide food effect information on the tablet formulation.

Additional Comment:

We note that your questions make reference to submission of pirfenidone film-coated tablets as a supplemental New Drug Application (sNDA). We remind you that an application with a new dosage form constitutes a new NDA. To prevent duplication of data that has been previously submitted, you may cross-reference relevant data from the pirfenidone capsules NDA, if necessary. Refer to the Guidance for Industry: *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees*. You may contact the User Fee staff if you have any further questions regarding this issue.

Nonclinical Comment:

As applicable for any differences between the capsule and tablet formulations, provide structures of any impurities and degradants of the drug substance and drug product in your IND submission. Monitor impurities and degradation products of all active ingredients and refer to ICH Guidance [ICH Q3A(R) and ICH Q3B(R)] for possible qualification requirements. Impurities or degradants of active ingredients that are identified as structural alerts should be at or below acceptable qualification thresholds to support an IND or NDA as described in the ICH *M7 Guideline, Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* (Step 4 Version dated June 23, 2014).

3.0

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

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/s/

JESSICA K LEE
05/27/2015