

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022535Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 022535

SUPPL #

HFD #

Trade Name Esbriet

Generic Name pirfenidone

Applicant Name InterMune, Inc.

Approval Date, If Known October 15, 2014

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES  NO

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

505(b)(1)

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

YES  NO

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

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

d) Did the applicant request exclusivity?

YES  NO

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

5 years

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

YES  NO

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

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

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

YES  NO

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

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES  NO

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES  NO

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

NDA#

NDA#

NDA#

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

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

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

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

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

YES  NO

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

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

YES  NO

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

YES  NO

If yes, explain:

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

YES  NO

If yes, explain:

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

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 #2 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: 10/8/14

Name of Office/Division Director signing form: Badrul A. Chowdhury, MD, PhD  
Title: Director, Division of Pulmonary, Allergy, and Rheumatology Products

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JESSICA K LEE  
10/15/2014

BADRUL A CHOWDHURY  
10/15/2014

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 022535 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: capsules		Applicant: InterMune, 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)		<b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b> <ul style="list-style-type: none"> <li><b>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</b></li> <li><b>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</b> <ul style="list-style-type: none"> <li><input type="checkbox"/> No changes</li> <li><input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i></li> </ul> </li> </ul> Date of check:
<b>❖ Actions</b>		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>11/23/14</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions <i>(specify type and date for each action taken)</i></li> </ul>		<input type="checkbox"/> None   CR 5/4/10
<b>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?</b> Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received
<b>❖ Application Characteristics<sup>3</sup></b>		

<sup>1</sup> 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.

<sup>2</sup> 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).

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

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

- Fast Track  Rx-to-OTC full switch  
 Rolling Review  Rx-to-OTC partial switch  
 Orphan drug designation  Direct-to-OTC  
 Breakthrough Therapy designation

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

- BLAs: Subpart E  
 Accelerated approval (21 CFR 601.41)  
 Restricted distribution (21 CFR 601.42)  
 Subpart H  
 Approval based on animal studies

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

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

Comments:

❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• 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.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) CR 5/4/10; AP 10/15/14
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)</li> </ul>	<input type="checkbox"/> Included
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<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"> <li>Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)</li> </ul>	<input type="checkbox"/> Included
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Labels ( <b>full color</b> carton and immediate-container labels) ( <i>write submission/communication date on upper right of first page of each submission</i> )	
<ul style="list-style-type: none"> <li>Most-recent draft labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
<ul style="list-style-type: none"> <li>Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>Review(s) (<i>indicate date(s)</i>)</li> </ul>	2/12/10 2/12/10 8/11/14 Acceptable 8/12/14
❖ Labeling reviews ( <i>indicate dates of reviews</i> )	RPM: <input type="checkbox"/> None 12/31/2009; 7/8/14 DMEPA: <input type="checkbox"/> None 4/15/10; 8/20/14 DMPP/PLT (DRISK): <input type="checkbox"/> None 8/20/14 OPDP: <input type="checkbox"/> None 4/5/2010; 8/18/14 SEALD: <input type="checkbox"/> None 4/1/2010 CSS: <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> None
<b>Administrative / Regulatory Documents</b>	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting ( <i>indicate date of each review</i> )	12/31/2009
❖ 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 only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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

<ul style="list-style-type: none"> <li>This application is on the AIP             <ul style="list-style-type: none"> <li>If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>Pediatrics (<i>approvals only</i>)             <ul style="list-style-type: none"> <li>Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>Orphan Exemption</u></li> </ul> </li> </ul>	N/A
<ul style="list-style-type: none"> <li>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, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)</li> </ul>	11/18/09; 12/11/09; 12/16/09; 12/18/09; 12/29/09; 1/6/10; 1/11/10; 1/15/10; 1/22/10; 1/27/10; 1/27/10; 1/29/10; 2/3/10; 2/4/10; 2/26/10; 3/3/10; 3/4/10; 3/12/10; 3/29/10; 4/12/10; 5/28/14; 6/5/14; 6/17/14; 7/17/14; 8/21/14; 8/27/14; 9/11/14; 9/30/14; 10/9/14; 10/14/14
<ul style="list-style-type: none"> <li>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)</li> </ul>	2/3/2010
<ul style="list-style-type: none"> <li>Minutes of Meetings             <ul style="list-style-type: none"> <li>If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> <li>Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> <li>EOP2 meeting (<i>indicate date of mtg</i>)</li> <li>Mid-cycle Communication (<i>indicate date of mtg</i>)</li> <li>Late-cycle Meeting (<i>indicate date of mtg</i>)</li> <li>Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> N/A or no mtg Meeting on 3/9/2011 under IND 67,284. Also preliminary comments sent on 4/30/2012 under IND 67,284 for resubmission. Meeting cancelled after Intermune received preliminary comments.  <input type="checkbox"/> No mtg 9/17/2008 <input type="checkbox"/> No mtg 12/14/2004 <input type="checkbox"/> N/A <input type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>Advisory Committee Meeting(s)             <ul style="list-style-type: none"> <li>Date(s) of Meeting(s)</li> </ul> </li> </ul>	<input type="checkbox"/> No AC meeting  3/9/2010
<b>Decisional and Summary Memos</b>	
<ul style="list-style-type: none"> <li>Office Director Decisional Memo (<i>indicate date for each review</i>)</li> <li>Division Director Summary Review (<i>indicate date for each review</i>)</li> <li>Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)</li> <li>PMR/PMC Development Templates (<i>indicate total number</i>)</li> </ul>	<input type="checkbox"/> None 5/4/2010; 10/15/14 <input type="checkbox"/> None 5/4/2010; 10/10/14 <input type="checkbox"/> None 4/23/2010; 10/9/14 <input checked="" type="checkbox"/> None
<b>Clinical</b>	
<ul style="list-style-type: none"> <li>Clinical Reviews             <ul style="list-style-type: none"> <li>Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> <li>Clinical review(s) (<i>indicate date for each review</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> No separate review see CDTL Memo  1/8/10; 4/1/10; 10/9/14 CDTL Rev

• Social scientist review(s) (if OTC drug) (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (indicate date of review/memo)	Clinical review 4/1/10 CDTL Review 10/9/14
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review)	<input type="checkbox"/> None OSE/Hepatology 9/23/14
❖ 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"> <li>• REMS Documents and REMS Supporting Document (indicate date(s) of submission(s))</li> <li>• REMS Memo(s) and letter(s) (indicate date(s))</li> <li>• 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)</li> </ul>	11/4/2009  <input type="checkbox"/> None 4/26/2010, 10/6/2014
❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)	<input type="checkbox"/> None requested 4/7/2010
<b>Clinical Microbiology</b> <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
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> No separate review
Statistical Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> No separate review
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None 1/11/2010; 4/5/2010; 9/3/14
<b>Clinical Pharmacology</b> <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 12/31/09; 4/5/10; 9/2/14
❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	<input type="checkbox"/> None requested
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input type="checkbox"/> No separate review 5/3/10; 8/20/14
• Supervisory Review(s) (indicate date for each review)	<input type="checkbox"/> No separate review 4/9/2010;
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None 12/15/09; 2/24/10; 4/5/10; 4/5/10; 4/5/10; 8/13/14; 8/14/14; 8/24/14
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input type="checkbox"/> No carc 4/1/10
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None 2/24/10 Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	<input checked="" type="checkbox"/> None requested

<b>Product Quality</b>		<input type="checkbox"/> None
<b>❖ Product Quality Discipline Reviews</b>		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> No separate review 5/3/10; 10/8/14
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> No separate review 4/9/10
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		<input type="checkbox"/> None 1/13/10; 4/5/10; 4/23/10; 9/2/14; 9/16/14
<b>❖ Microbiology Reviews</b>		<input type="checkbox"/> Not needed 3/25/10; 5/3/10; 8/14/14
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>		
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		
<b>❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i></b>		<input checked="" type="checkbox"/> None
<b>❖ Environmental Assessment (check one) (original and supplemental applications)</b>		
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		See CMC review 4/5/10
<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>		
<b>❖ Facilities Review/Inspection</b>		
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do <b>NOT</b> include EER Detailed Report; date completed must be within <b>2 years</b> of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>5</sup>)</i>		Date completed: <input checked="" type="checkbox"/> Acceptable 3/8/10; 9/11/14 <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within <b>30 days</b> of action date) <i>(original and supplemental BLAs)</i>		Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<b>❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i></b>		<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

<sup>5</sup> i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

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

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/s/  
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JESSICA K LEE  
10/15/2014

Dear Dr. L'Italien:

Your submission dated May 23, 2014, is currently under review. Attached are our revisions to your proposed package insert (PI) and patient information leaflet submitted October 10, 2014. Be advised that these labeling changes are not the Agency's final recommendations and that additional labeling changes may be forthcoming as the labeling review continues.

We request for your concurrence of the attached label as soon as possible, but no later than close of business today, October 14, 2014. Submit a clean and track-change versions of the label. The information can be sent by electronic mail to [Jessica.Lee@fda.hhs.gov](mailto: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.

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/s/  
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JESSICA K LEE  
10/14/2014

Dear Dr. L'Italien:

Your submission dated May 23, 2014, is currently under review. Attached are our revisions to your proposed package insert (PI) and patient information leaflet submitted October 7, 2014. Comments regarding some changes are embedded within the product label. Be advised that these labeling changes are not the Agency's final recommendations and that additional labeling changes may be forthcoming as the labeling review continues.

We request you address the deficiencies/edits and submit the corrected draft label as soon as possible, but no later than noon, Friday, October 10, 2014. Submit a clean and track-change versions of the label. The information can be sent by electronic mail to [Jessica.Lee@fda.hhs.gov](mailto: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.

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/s/

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JESSICA K LEE  
10/09/2014

Dear Dr. L'Italien:

Your submission dated May 23, 2014, is currently under review. Attached are our revisions to your proposed package insert (PI) and patient information leaflet submitted September 4, 2014. Comments regarding some changes are embedded within the product label. Be advised that these labeling changes are not the Agency's final recommendations and that additional labeling changes may be forthcoming as the labeling review continues.

We request you address the deficiencies/edits and submit the corrected draft label as soon as possible, but no later than noon, Monday, October 6, 2014. Submit a clean and track-change versions of the label. The information can be sent by electronic mail to [Jessica.Lee@fda.hhs.gov](mailto: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.

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/s/

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JESSICA K LEE  
09/30/2014

Your submission dated, May 23, 2014, to NDA 22-535, is currently under review. We have the following request for information:

Provide the hazard ratio, 95% confidence interval, and p-value for the pooled analysis of time to death (as measured at vital status – end of study) in studies 004, 006, and 016, as indicated in the highlighted portion of the table below.

<b>Survival Analysis of All-Cause Mortality at Vital Status – End of Study: Studies 016, 004, and 006</b>			
	<b>Number of Events (%)</b>		
<b>All-cause death</b>	<b>Pirfenidone 2403mg/day</b>	<b>Placebo</b>	<b>Hazard Ratio<sup>†</sup> (95% CI), p value<sup>‡</sup></b>
<b>Study 016</b>	<b>N=278</b>	<b>N=277</b>	
<b>Death</b>	11 (4.0)	20 (7.2)	0.55 (0.26, 1.15), p=0.105
<b>Study 004</b>	<b>N = 174</b>	<b>N = 174</b>	
<b>Death</b>	14 (8.0)	20 (11.5)	0.68 (0.34, 1.34), p=0.268
<b>Study 006</b>	<b>N = 171</b>	<b>N = 173</b>	
<b>Death</b>	18 (10.5)	17 (9.8)	1.06 (0.55, 2.07), p=0.856
<b>Pooled Studies 004/006/016</b>	<b>N=623</b>	<b>N=624</b>	
<b>Death</b>	43 (6.9)	57 (9.1)	

<sup>†</sup> Hazard ratio was based on the Cox proportional hazard model, with geographic region (USA and ROW) as a factor.  
<sup>‡</sup> p-value based on log-rank test, stratified by geographic region (USA and ROW) comparing pirfenidone 2403 mg/d to placebo

Provide your response as soon as possible. The information can be sent by electronic mail to [Jessica.Lee@fda.hhs.gov](mailto: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.

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/s/

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JESSICA K LEE  
09/11/2014

Dear Dr. L'Italien:

Your submission dated May 23, 2014, is currently under review. Attached are our revisions to your proposed package insert (PI) and patient information leaflet. Comments regarding some changes are embedded within the product label. The following comments provide additional clarification as to some of the changes made in the attached label. The FDA-proposed insertions are underlined, deletions are in strike-out, and comments are included adjacent to the labeling text. Be advised that these labeling changes are not the Agency's final recommendations and that additional labeling changes will be forthcoming as the labeling review continues.

**Comments Pertaining to Carton/Container Labeling**

**A. All Container Labels and Carton Labeling**

1. The trade name and established name is listed at the top and bottom of the label and labeling. Consider deleting the presentation at the bottom of the label and labeling, as it is redundant information.

**General Comments Pertaining to the Package Insert**

2. Sections in the package insert that relate to liver safety and monitoring are under active review and a topic of internal discussion at the current time. Further revisions to these sections will be forthcoming as the labeling review continues.
3. For ease of communication, Studies 016, 004, and 006 are designated as Studies 1, 2 and 3, respectively, in the package insert.

**Comments Pertaining to Specific Sections of the Package Insert**

4. Section 14: Clinical Studies
  - This section was substantially reorganized to be presented by efficacy variable. Figure 1 has been added to show a cumulative responder distribution of change from baseline in percent-predicted forced vital capacity, (b) (4). Descriptions of the results at a threshold of 10% FVC decline are included in the text.
  - (b) (4)
  - Reporting of (b) (4) removed as the (b) (4) were (b) (4)
  - The (b) (4) information regarding death is a clinically important endpoint in IPF and warrants reporting in the package insert. Therefore, the format has been changed to

include the frequencies of death in each individual study, [REDACTED] (b) (4)

We request you address the deficiencies/edits and submit the corrected draft label by COB, September 3, 2014. Submit a clean and track-change versions of the label. The information can be sent by electronic mail to [Jessica.Lee@fda.hhs.gov](mailto: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.

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JESSICA K LEE  
08/27/2014

Your submission dated, May 23, 2014, to NDA 22-535, is currently under review. We have the following request for information:

In PSUR 4 [covering the time period of September 1, 2012 to February 27, 2013], p. 762, your submission includes a letter from Dr. [REDACTED]<sup>(b) (4)</sup>, and his review of four potential Hy's law cases: MCN201301IM003105, MCN2004IM000967, MCN201212IM002980, and MCN201201IM002302.

Please submit the same information that was provided to Dr. [REDACTED]<sup>(b) (4)</sup> (and any additional information that may have been acquired after his review) for each of the cases.

Provide your response as soon as possible. The information can be sent by electronic mail to [Jessica.Lee@fda.hhs.gov](mailto: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.

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/s/

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JESSICA K LEE  
08/21/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

NDA 022535

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

InterMune, Inc.  
3280 Bayshore Boulevard  
Brisbane, CA 94005

ATTENTION: James L'Italien, Ph.D.  
Senior Vice President, Regulatory Affairs and Quality Assurance

Dear Dr. L'Italien:

Please refer to your New Drug Application (NDA) dated May 23, 2014, received May 23, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pirfenidone Capsules, 267 mg.

We also refer to your May 29, 2014, correspondence, received May 29, 2014, 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 acceptable.

If any of the proposed product characteristics as stated in your May 29, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nichelle Rashid, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application, contact Jessica Lee, Regulatory Project Manager in the Office of New Drugs, at (301) 796-3769.

Sincerely,

*{See appended electronic signature page}*

Kellie A. Taylor, Pharm.D., MPH  
Deputy Director  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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TODD D BRIDGES on behalf of KELLIE A TAYLOR  
08/12/2014



NDA 022535

**GRANT –  
BREAKTHROUGH THERAPY DESIGNATION**

InterMune, Inc.  
3280 Bayshore Blvd.  
Brisbane, CA 94005

Attention: James L'Italien, PhD  
Senior Vice President  
Regulatory Affairs and Quality Assurance

Dear Dr. L'Italien:

Please refer to your New Drug Application (NDA) resubmission, dated and received May 23, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for pifrenidone.

We also refer to your June 6, 2014, request for Breakthrough Therapy designation. We have reviewed your request and have determined that pifrenidone for Idiopathic Pulmonary Fibrosis (IPF) meets the criteria for Breakthrough Therapy designation. Therefore, we are granting your request for Breakthrough Therapy designation. Please note that if the clinical development program does not continue to meet the criteria for Breakthrough Therapy designation, we may rescind the designation.

For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*.<sup>1</sup>

If the breakthrough therapy designation for pifrenidone for IPF is rescinded, submission of portions of the NDA will not be permitted under this program. However, if you have Fast Track designation you will be able to submit portions of your application under the Fast Track program.

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

---

<sup>1</sup> <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

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/  
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BADRUL A CHOWDHURY  
07/17/2014



NDA 022535

**ACKNOWLEDGE -  
BREAKTHROUGH THERAPY REQUEST**

InterMune, Inc.  
3280 Bayshore Blvd.  
Brisbane, CA 94005

Attention: James L'Italien, Ph.D.  
Senior Vice President  
Regulatory Affairs and Quality Assurance

Dear Dr. L'Italien:

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

We acknowledge receipt on June 6, 2014, of your June 6, 2014, request for Breakthrough Therapy designation submitted under section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) for Idiopathic Pulmonary Fibrosis (IPF). We are reviewing your request and will respond to you within 60 days of the receipt date. We will contact you if we have any questions or require additional information.

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

Sincerely,

*{See appended electronic signature page}*

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

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/s/

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JESSICA K LEE  
06/17/2014



NDA 022535

**ACKNOWLEDGE –  
CLASS 2 RESUBMISSION**

InterMune, Inc.  
3280 Bayshore Blvd.  
Brisbane, CA 94005

Attention: James L'Italien, PhD  
Senior Vice President  
Regulatory Affairs and Quality Assurance

Dear Dr. L'Italien:

We acknowledge receipt on May 23, 2014, of your May 23, 2014, resubmission to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for pifrenidone.

We consider this a complete, class 2 response to our May 4, 2010, action letter. Therefore, the user fee goal date is November 23, 2014.

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

Sincerely,

*{See appended electronic signature page}*

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

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/s/

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JESSICA K LEE  
06/05/2014



IND 67284

**MEETING PRELIMINARY COMMENTS**

InterMune, Inc.  
3280 Bayshore Boulevard  
Brisbane, CA 94005

Attention: Marianne Porter, Ph.D.  
Senior Vice President, Chief Regulatory and Drug Safety Officer

Dear Dr. Porter:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for pirfenidone capsules at 267mg.

We also refer to your February 10, 2012, correspondence, received February 13, 2012, requesting a meeting to discuss proposed statistical analysis plans for the Integrated Summary of Safety and Integrated Summary of Effectiveness, as well as gain agreement with the Agency on the structural format and content of the Class 2 resubmission for pirfenidone.

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for May 02, 2012, 2:00PM, between InterMune and the Division of Pulmonary, Allergy, and Rheumatology Products. 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. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting

## Clinical

1. *Clinical Datasets: Does the FDA concur with the proposed structure, format and standard as described in Section 9.1.2 for clinical datasets?*

**FDA Response:** You propose to use the same dataset structure, format, and standards for PIPF-016 in the resubmission as that of PIPF-004 and PIPF-006 in the original NDA. We concur. Submit the SAS codes that were used to create the analysis dataset and to generate the main efficacy analysis results.

2. *SAP for PIPF-016: Does the FDA concur with InterMune's proposed statistical analysis plan for the confirmatory study, PIPF-016, as provided in Appendix 1?*

**FDA Response:** We concur. Submit the SAS codes that were used to create the analysis dataset and to generate the main efficacy analysis results.

3. *Resubmission Safety Update and SAP: The Resubmission Safety Update will focus on any clinically meaningful changes in the safety profile of pirfenidone (established in the original NDA) based on new information and data obtained from the confirmatory study, PIPF-016, and long-term safety studies. Does the FDA concur with InterMune's proposed Resubmission Safety Update (Section 9.2.5), including the statistical analysis plan as provided in Appendix 2?*

**FDA Response:** We concur. Submit the SAS codes that were used to create the analysis dataset and to generate the inferential analysis results.

4. *SAP for resubmission ISE: The statistical analysis plan for the resubmission ISE focuses on the integration of data and results of the confirmatory study, PIPF-016, into the existing body of evidence to address the CRL. Does the FDA concur with InterMune's proposed statistical analysis plan for the resubmission ISE as provided in Appendix 3?*

**FDA Response:** You have defined disease progression as a 6MWT decline of (b) (4) (b) (4) Use of (b) (4) for the 6MWT as the definition of disease progression will be a review issue. Include both progression free survival event variables based on the new definition (6MWT) and the old definition (DLco) for studies PIPF-004 and PIPF-006 along with two flag variables indicating which criteria were met for the progression free survival event.

As a sensitivity analysis to the primary efficacy endpoints (i.e. %predicted FVC), please provide an analysis comparing the slopes of the two treatment groups at week 52 for each study (PIPF-004, PIPF-006, and PIPF-016).

Submit the SAS codes that were used to create the analysis dataset and to generate the main efficacy analysis results

## Clinical and Regulatory

1. *Resubmission eCTD: Does the FDA concur with InterMune's proposed structural format and key contents of the resubmission eCTD as described in Section 9 and Appendix 4 of this briefing document?*

**FDA Response:** Yes, we agree.

## Regulatory

1. *Class 2 Resubmission: InterMune would like to confirm that the resubmission, with the format and contents as proposed in this briefing document, will be a Class 2 resubmission with a PDUFA review period of 6 months from the date of FDA's receipt of the submission?*

**FDA Response:** Yes, we agree.

2. *Guidance for Resubmission: Does the FDA have any additional guidance in regards to the organization of the resubmission that may potentially facilitate their review?*

**FDA Response:** We have no further guidance at this time.

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.

If you have any questions, call me, at (301) 796-3367.

Sincerely,

*{See appended electronic signature page}*

Leila P. Hann  
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/  
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LEILA P HANN  
04/30/2012

## Rashid, Nichelle E

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**From:** Rashid, Nichelle E  
**Sent:** Wednesday, May 28, 2014 2:37 PM  
**To:** stripathi@intermune.com  
**Cc:** Rashid, Nichelle E; Bradley, Sean; Kang, Sue  
**Subject:** Request for Proprietary Name Review/ NDA 22535/ Pirfenidone Capsules

Dear Dr. L'Italien,

Reference is made to your New Drug Application submitted to the Agency for "Pirfenidone Capsules." Reference is also made to your Request for Proprietary Name Review received on May 5, 2014. The Division of Medication Error Prevention and Analysis (DMEPA) request that you resubmit your Request for Proprietary Name Review since the application was under Complete Response status when it was submitted. We encourage you to resubmit your request as soon as possible in order to allow ample time to work with you in finding an acceptable name for your proposed product.

If you have any questions in regards to your proprietary name submission, please do not hesitate to contact me.

Kind regards,

**Nichelle E. Rashid**  
Senior Safety Regulatory Health Project Manager  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
**Tel: (301) 796-3904**  
Fax: (301) 796-9725  
[nichelle.rashid@fda.hhs.gov](mailto:nichelle.rashid@fda.hhs.gov)

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/s/  
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NICHELLE E RASHID  
05/28/2014



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

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**Meeting Type:** Type C  
**Meeting Date and Time:** March 9, 2011  
**Meeting Location:** White Oak Campus Bldg 22 Room 1417  
**Application Number:** IND 67284  
**Product Name:** pirfenidone  
**Received Briefing Package** February 2, 2011  
**Sponsor Name:** InterMune  
**Meeting Requestor:** Marianne Armstrong Porter  
**Meeting Chair:** Badrul A. Chowdhury  
**Meeting Recorder:** Eunice H. Chung-Davies

**Meeting Attendees:**

**FDA Attendees**

Badrul Chowdhury, M.D., Ph.D., Director, Division of Pulmonary, Allergy, and Rheumatology Products

Sally Seymour, M.D., Deputy Director for Safety, Division of Pulmonary, Allergy, and Rheumatology Products

Banu Karimi-Shah, M.D., Clinical Reviewer, Division of Pulmonary, Allergy, and Rheumatology Products

Theresa Michele, M.D., Clinical Team Leader, Division of Pulmonary, Allergy, and Rheumatology Products

Feng Zhou, M.S., Statistics Reviewer, Division of Biometrics II

Joan Buenconsejo, Ph.D., Acting Statistics Team Leader, Division of Biometrics II

Eunice Chung-Davies, Pharm.D., Sr. Regulatory Management Officer, Division of Pulmonary, Allergy, and Rheumatology Products

**Sponsor Attendees**

Marianne Armstrong Porter, Ph.D., Senior Vice-President, InterMune

Bill Bradford, M.D., Ph.D., Senior Vice-President, Clinical Affairs, InterMune

Teresa Coleman, Sr. Director, Regulatory Affairs, InterMune

Spencer Hudson, Ph.D., Vice-President, Biometrics, InterMune

Steve Porter, M.D., Ph.D., Chief Medical Officer, Senior Vice President, InterMune

(b) (4)

**1.0 BACKGROUND**

Dr. Marianne Armstrong Porter of InterMune requested a Type C meeting to discuss a Phase 3 program to support approval of NDA 22-535 designed to address the issues articulated by the Agency in the Complete Response letter dated May 4, 2010. The Type C meeting was granted. Preliminary responses were provided to InterMune on Tuesday, March 8, 2011. Any discussion that occurred is summarized below in normal font.

**2.0 DISCUSSION*****Clinical:***

***PIPF-016 is designed as a confirmatory double-blind, placebo-controlled, multicenter study in which 500 patients with IPF will be randomized to receive either pirfenidone 2403 mg/day or placebo in a 1:1 ratio using block randomization. Compared with PIPF-004 and PIPF-006, the eligibility criteria have been slightly modified in order to enroll a population with a greater likelihood of disease progression, including permitting patients with percent predicted DLco as low as 30% to enter the study. The primary endpoint of PIPF-016 is the change from baseline to Week 52 in percent predicted FVC. Key secondary endpoints are 6MWT distance change at Week 52 and progression-free survival. The draft clinical study protocol is attached as Appendix 2.***

***Question 1:***

***Could successful achievement of the primary efficacy endpoint in PIPF-016, including evidence of a clinically meaningful response and a favorable responder analysis, support the approval of the proposed indication for pirfenidone for the treatment of patients with IPF to reduce decline in lung function?***

***FDA Response:***

*In general, successful achievement of the primary efficacy endpoint in PIPF-016 could support approval of the proposed indication provided that the all-cause mortality results of this trial and the pooled all-cause mortality results (with PIPF-004 and 006) demonstrate supportive evidence of benefit. Ultimately, whether the submitted data support the proposed indication would be a review issue. We note that you are proposing to analyze the primary endpoint at an earlier time point (52 weeks) in PIPF-016. This is concerning because PIPF-006, when analyzed near this time point (48 weeks), showed a statistically positive effect for pirfenidone that did not persist at 72 weeks, thus raising questions regarding the durability of the treatment effect. Shortening the treatment duration to 52 weeks introduces risk into your program, should a mortality benefit not be demonstrated at this time point. For these reasons, we encourage you to extend PIPF-016 to 72 weeks and analyze the primary endpoint at 72 weeks, as you did in the completed Phase 3 trials.*

Discussion:

InterMune indicated their intention to submit a class 2 resubmission and wished to obtain clarity on the Division's response to Question 1 and the additional comment regarding adjudication of deaths. They wished to better understand what the Division considers to be supportive evidence of benefit. The Division summarized those outcomes which would be acceptable as providing evidence of benefit: 1) the proposed study shows a statistically significant decrease in mortality in pirfenidone treated patients, or 2) pooling of studies 004, 006, and 016 demonstrates a statistical benefit on mortality. Other outcomes that might be considered as being supportive evidence of benefit would be a review issue. The Division stated that when studies 004 and 006 are pooled, the point estimates for mortality are favorable. For this reason, the Division hoped that the sponsor might be able to show a statistically significant decrease in mortality with more patients.

The Division further indicated their preference for the 72 week endpoint and indicated their dislike with the 52 week endpoint due to results of their previous Phase III study in which benefit observed at 52 weeks was lost at 72 weeks. InterMune reiterated that study 016 is not powered to detect a statistically significant decrease in mortality, regardless of the duration (52 vs. 72 weeks) because deaths are not common in the mild-to-moderate IPF population that will be studied. In addition, InterMune noted that based upon their calculations, the pooled data for 004, 006, and 016 will not be powered to show a statistically significant difference for mortality either.

The Division strongly recommended that InterMune consider a 72 week study. InterMune asked if it would be supportive if their 72 week study showed positive results on the primary FVC endpoint and there was a directional benefit on (all cause) mortality. The Division believed this to be the most straightforward path because a win with a 72 week study would provide for convincing replication of results. A shorter study, as proposed, would need to provide more robust results in terms of mortality.

InterMune proposed

(b) (4)

(b) (4)

The Division

suggested that InterMune submit their rationale for choosing this analytical approach and also requested that they conduct an analysis on the study 006 data using the proposed approach, and the Division will provide feedback in the post meeting notes. InterMune stated that they would submit these results within a week.

**Post-meeting notes:** : Intermune was unable to provide the 72 week analytical method that was discussed at the meeting in time to make it in before our 30 day deadline for meeting minutes. They will provide the information as soon as it is available. Although the proposed statistical approach may be reasonable, whether we can rely on the proposed analysis is dependent on the Sponsor's analysis of the existing data. As a result, no agreement can be reached as to the acceptability of the proposed statistical analysis plan at this point in time.

**Question 2:**

***Several recent reports demonstrate the clinical validity and utility of 6MWT***

***distance in patients with IPF, including those that find excellent reproducibility (Eaton 2005), significant correlation with FVC or DLco (Eaton 2005; Caminati 2009), and strong associations with survival (Hallstrand 2005, Lettieri 2006, Lederer 2006, Caminati 2009, du Bois 2010).***

***Three reports calculate the minimal clinically important difference, with results ranging from 28 to 45 meters (Holland 2009, Swigris 2010, du Bois 2010) (see Appendix 3 for copies of cited references).***

(b) (4)

***FDA Response:***

(b) (4)

***However, we encourage you to include this endpoint in your clinical trials. Clarify whether the 6MWT will be conducted according to American Thoracic Society (ATS) standards.***

No discussion required.

**Question 3:**

***The protocol for PIPF-016 includes a conservative interim stopping boundary formortality to guide the DMC and protect the interests of participating patients (seeProtocol Section 5.5 in Appendix 2). If the stopping boundary is crossed following the completion of study enrollment and the study is terminated,*** (b) (4)

*FDA Response:*

*Your proposal to conduct interim analyses on mortality and apply an alpha level of 0.0001 appears reasonable provided that the analyses are conducted for all-cause mortality. Clarify when you plan to conduct these interim analyses. Include the Data Monitoring Committee (DMC) charter when you submit your protocol for review. This charter should include well-defined standard operation procedures with detailed logistics and procedures to be used to ensure the integrity of the trial. Refer to the Guidance on the Establishment and Operation of the Clinical Trial Data Monitoring Committees for more information.*

(b) (4)

*Refer to our additional comment regarding adjudication of the cause of death.*

No discussion required.

*Additional Clinical Comments*

- 1. The proposed protocol should include a pre-specified plan to adjudicate the cause of deaths that occur during the course of the trial. The adjudication of cause of death should be carried out by an independent adjudication committee, rather than be left to individual investigator discretion.*

*Discussion:*

*InterMune agrees to do this.*

- 2. Clarify the location (i.e. countries) in which the proposed study will enroll patients.*

*Additional Discussion:*

The Division asked about the timeframe to start the study. InterMune responded that they plan to have a final protocol by the end of the month, first patient in by June 2011, first patient enrolled by first quarter of 2012.

The Division asked where they would enroll patients. InterMune responded that they are looking into the U.S., Central and South America, Australia and New Zealand.

InterMune indicated some concern with conducting a 72 week vs. a 52 week study because there may be a risk of patients crossing over to commercial product due to pirfenidone approval status in other countries.

---

Eunice H. Chung-Davies  
Regulatory Project Manager  
301-796-4006

### **3.0 ISSUES REQUIRING FURTHER DISCUSSION**

N/A

### **4.0 ACTION ITEMS**

N/A

### **5.0 ATTACHMENTS AND HANDOUTS**

Handout attached

Drafted by: Eunice Chung-Davies/March 14, 2011

Initialed by:

Banu Karimi-Shah/21MAR2011

Terri Michele/6APR2011

Joan Buenconsejo/23MAR2011

Sally Seymour/7APR2011

Badrul Chowdhury/7APR2011

Finalized by: Eunice Chung-Davies/7APR2011

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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EUNICE H CHUNG-DAVIES  
04/07/2011

Your submission dated November 4, 2009, received November 4, 2009, to NDA 22-535, is currently under review. We have the following requests for information:

1. Regarding the microbial Limits Testing Method and validation for pirfenidone capsules:
  - a.) Provide methods 070001-00, 070002-00 and 070005-00 referenced in the (b) (4) of (b) (4) validation protocol MV24081308 or a detailed description of those methods.
  - b.) Provide data summaries and rationale justifying the use of (b) (4) and (b) (4) dilutions for testing drug product for microbial limits, the basis for selecting a (b) (4) method in lieu of other recommended methods such as filtration and the amount of product actually sampled for this test. Provide a calculation of the sensitivity of your recommended method. Indicate whether this method would detect (b) (4) cfu/g.
  - c.) The data appears to conflict between the TAC and Y&M validation studies and the specified organism studies. Three of the test bacteria are detected at the (b) (4) level in one study and not in the other. Explain this observation.
2. The drug substance contains the impurity (b) (4). This impurity is a potential mutagen existing at a level that causes more than 1.5 µg/day total exposure allowed by the draft genotoxic guidance. Responses from the DMF (b) (4) holder received on February 18, 2010 are inadequate to resolve the issue. An information request was again sent to the DMF holder on March 12, 2010. This issue is outstanding.
3. The font used for the dosage form and strength next to the commercial name at the right corner of each package carton is too small. Dosage form and strength information should be physically located close to the product name on the top left corner of each packaging carton.
4. The symbolic markings 1 and 2 of the carton opening instructions are not easy to read due to low contrast to the background color.
5. (b) (4)
6. (b) (4)
7. The capsule tray does not contain product identification and dosage information. This can be a potential problem if the patient takes the capsule tray out and discards the carton.
8. Modify the capsule blister packaging by using a (b) (4) blister packaging. The sample provided does not appear to be (b) (4) (b) (4) is inadequate.

9. Changes to the specifications will require a supplement. Provide and agreement to submit a CBE-30 supplement when you revise the drug substance and drug product total impurities specifications.

Submit your responses to me via telephone facsimile to 301-796-9728 or email at [Eunice.Chung@fda.hhs.gov](mailto:Eunice.Chung@fda.hhs.gov) by COB April 7, 2010. Your responses will subsequently needs to be submitted officially to the NDA. If you have any questions, please contact Eunice Chung, Regulatory Project Manager, at 301-796-4006.

NDA 22-535

Drafted by: XShen/25MAR2010  
Initialed by: Prasad Peri/29MAR2010  
SBarnes/26MAR2010

Finalized by: EChung/29MAR2010

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22535	ORIG-1	INTERMUNE INC	Esbriet (pirfenidone capsules)

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/s/

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EUNICE H CHUNG  
03/29/2010

Your submission dated November 4, 2009, received November 4, 2009, to NDA 22-535, is currently under review. We have the following requests for information:

1. Provide the amount (in mass) of ink printed on each capsule.
2. In two of the blister packaging configurations, each blister cell contains (b) (4) Clarify if you observed in your stability studies (including accelerated conditions) (b) (4) Clarify your controls to assure the correct number of capsules in each blister cell.
3. Provide packaging carton samples.

Submit your responses to me via telephone facsimile to 301-796-9728 or email at [Eunice.Chung@fda.hhs.gov](mailto:Eunice.Chung@fda.hhs.gov) by COB March 19, 2010. Your responses will subsequently needs to be submitted officially to the NDA. If you have any questions, please contact Eunice Chung, Regulatory Project Manager, at 301-796-4006.

NDA 22-535

Drafted by: XShen/10MAR2010  
Initialed by: Prasad Peri/10MAR2010  
SBarnes/12MAR2010

Finalized by: EChung/12MAR2010

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-22535	----- ORIG-1	----- INTERMUNE INC	----- Esbriet (pirfenidone capsules)

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EUNICE H CHUNG  
03/12/2010

Your submission dated November 4, 2009, to NDA 22-535, is currently under review and we have the following request for information:

1. Data sets for PK analysis
  - a. Provide a data file containing time-ordered records of doses and concentrations used for the non-compartmental PK analysis of PIPF-005. The data file should be in SAS transport files (.xpt format). Provide associated data definition file.

Please provide a response by COB March 8, 2010 in the most expedited method. The response will have to be submitted officially to the NDA as well.

---

Eunice Chung  
Regulatory Management Officer

Drafted by: EShang/3MAR2010  
Initialed by: Sbarnes/4MAR2010  
YXu/3MAR2010

Finalized by: Echung/4MAR2010

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22535	ORIG-1	INTERMUNE INC	Esbriet (pirfenidone capsules)

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/s/

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EUNICE H CHUNG  
03/04/2010

Your submission dated November 4, 2009, to NDA 22-535, is currently under review. In your January 21, 2010, submission, you requested clarification on the Agency's Nonclinical comment 3. The following is our response:

Sponsor's question:

In summary, the sponsor has evaluated all known related substance process impurities for their genotoxic and carcinogenic potential in accordance with guidance to industry, and believes the four known impurities to be non-genotoxic and non-carcinogenic and to be adequately qualified. **To further address Non-clinical question 3 in the FDA filing letter the sponsor requests clarification on what is meant by the reference to "six (6) other potential impurities in the drug substance or drug product."**

FDA response:

Please refer to the DMF Holder [REDACTED] (b) (4) for the identities of the impurities with genotoxic structural alerts that were referenced in the 74 day letter. After review of DMF [REDACTED] (b) (4) dated January 22, 2010, we narrowed the list to 3 impurities that have potential safety concerns.

If you have any questions, please contact Eunice Chung, Regulatory Project Manager, at 301-796-4006.

Drafted by: Echung/25FEB2010  
Initialed by: SBarnes/26FEB2010  
TRobison/26FEB2010  
MShea/2MAR2010  
XShen/3MAR2010  
PPeri/3MAR2010

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22535	ORIG-1	INTERMUNE INC	Esbriet (pirfenidone capsules)

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/s/

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EUNICE H CHUNG  
03/03/2010

Your submission dated November 4, 2009, received November 4, 2009, to NDA 22-535, is currently under review. We have the following requests for information:

1. Include (b) (4) Table 3.2.P.3.4-1 or justify that it is not critical.
2. We recommend that you retain the (b) (4)
3. Your appearance method (b) (4)
4. In the third paragraph of Section 3.2.P.5.2 on page 5 of 40, the statement (b) (4)  
Rectify the error.
5. Your impurity analysis method validation report TTP-IFL-J0030 (page 19 of 27) shows (b) (4) for each of the four identified impurities. It (b) (4) dependent on the individual impurity (for example, (b) (4) Rectify the method for impurity quantitation. Note that it may be acceptable to apply a correction factor in the calculations if the recoveries are consistent.
6. Your current drug product individual impurity specification of (b) (4) ” is not acceptable. Correct it to be as follows: each individual impurity  $\leq$  (b) (4) %, per ICH Q3B.
7. The total impurity specification of (b) (4) % for both drug substance and drug product is (b) (4) than actually observed impurity results. We recommend (b) (4) to reflect actual batch analysis and stability results.
8. Correct the drug product batch analysis impurity results from 0.00% to “Not Detected” or appropriate descriptor.
9. Clarify at what stage the imprinting of the capsule is performed. Justify the rationale of conducting drug product stability using capsules with (b) (4) instead of using the to be marketed product.
10. The dissolution specification in Table 3.2.P.8.1-2 is  $Q \geq$  (b) (4) %. However, in Section 3.2.P.8.1 Subsection 4.5 Dissolution you claim that the proposed dissolution acceptance criterion is “ $Q \geq$  (b) (4) % at 30 minutes”. Rectify the contradicting values of the acceptance criterion in the application.
11. Your dissolution results for all summarized packaging configurations and storage conditions indicate that the mean dissolution at 30 minutes was at least (b) (4) %. Neither of your proposed dissolution acceptance criterion properly reflect the typical dissolution performance even after storage for (b) (4)

(b) (4) Increase your criterion to allow discrimination power of product batch with possible sub-typical dissolution performance.

12. Provide mock up labeling for packaging cartons.

Submit your responses to me by COB March 10, 2010 via telephone facsimile to 301-796-9728 or email at [Eunice.Chung@fda.hhs.gov](mailto:Eunice.Chung@fda.hhs.gov). Your responses will subsequently need to be submitted officially to the NDA. If you have any questions, please contact Eunice Chung, Regulatory Project Manager, at 301-796-4006.

NDA 22-535

Drafted by: XShen/25FEB2010  
Initialed by: ASchroeder/25FEB2010  
PPrasad/26FEB2010  
Sbarnes/26FEB2010

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22535	ORIG-1	INTERMUNE INC	PIRFENIDONE CAPSULE

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EUNICE H CHUNG  
02/26/2010



NDA 022535

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

InterMune, Inc.  
3280 Bayshore Boulevard  
Brisbane, CA 94005

ATTENTION: Marianne Armstrong, PhD  
Chief Medical Affairs and Regulatory Officer, Senior Vice President

Dear Dr. Armstrong:

Please refer to your New Drug Application (NDA) dated November 4, 2009, received November 4, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pirfenidone Capsules, 267 mg.

We also refer to your November 18, 2009, correspondence, received November 19, 2009, 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 acceptable.

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

If **any** of the proposed product characteristics as stated in your November 18, 2009, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Carolyn Volpe, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5204. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Eunice Chung at 301-796-4006.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-22535	----- ORIG-1	----- INTERMUNE INC	----- PIRFENIDONE CAPSULE

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CAROL A HOLQUIST  
02/12/2010

Your submission dated November 4, 2009, to NDA 22-535, is currently under review. We have the following request for information:

1. Submit the narratives for all patients who died at anytime during the study, in a document organized in the following manner:

Narratives: Deaths At Any Time During The Study

A. Pirfenidone 1197 mg/day

1. IPF-related
2. Not IPF-related

B. Pirfenidone 2403 mg/day

1. IPF-related
2. Not IPF-related

C. Placebo

1. IPF-related
2. Not IPF-related

In addition, indicate which narratives represent patient deaths that were treatment-emergent.

2. Clarify the following:

A. Differences in the randomized patient subset in patients who discontinued due to AEs in Table 5-2 and Table 5-43 of the ISS.

**Table 5-2** Reasons for Early Discontinuation of Treatment in the Randomized Patient Subset and the Pirfenidone Patient Subset

Reason for Discontinuation of Study Treatment	Number of Patients, n (%)			
	Randomized Patient Subset			Pirfenidone Patient Subset
	Pirfenidone 1197 mg/d (N = 87)	Pirfenidone 2403 mg/d (N = 345)	Placebo (N = 347)	Pirfenidone Patients (N = 515)
Completed Study Treatment	70 (80.5%)	273 (79.1%)	285 (82.1%)	343 (66.6%)
PIPF-002 Patients Continuing Study Treatment <sup>a</sup>	NA	NA	NA	43 (8.3%)
Did Not Complete Study Treatment	17 (19.5%)	72 (20.9%)	62 (17.9%)	129 (25.0%)
AE or Unacceptable Toxicity	11 (12.6%)	45 (13.0%)	28 (8.1%)	78 (15.1%)

**Table 5-43** Adverse Events Leading to Early Discontinuation of Study Treatment in the Randomized Patient Subset

AEs Leading to Early Discontinuation	Number of Patients, n (%)		
	Pirfenidone 1197 mg/d (N = 87)	Pirfenidone 2403 mg/d (N = 345)	Placebo (N = 347)
System Organ Class Preferred Term ("Sex") <sup>a</sup>			
Patients with Any AE Leading to D/C	9 (10.3%)	51 (14.8%)	30 (8.6%)
Blood and Lymphatic System Disorders	0	1 (0.3%)	0
Bone Marrow Failure	0	1 (0.3%)	0

3. The Agency's statistical reviewer produced the following tables. Please verify the results. In addition, please send SAS program and output. Note: On-treatment denotes between 1<sup>st</sup> day of randomization and 28 days after the last dose of study drug (i.e. TRTENDT+28). Vital Status at End of Study denotes all deaths at any time.

Table 1. Survival Analysis on All Cause Mortality

	<i>Study 004</i>		<i>Study 006</i>		<i>Pooled Study 004/006</i>	
	<i>Pirfenidone (N=174)</i>	<i>Placebo (N=174)</i>	<i>Pirfenidone (N=171)</i>	<i>Placebo (n=173)</i>	<i>Pirfenidone (N=345)</i>	<i>Placebo (n=347)</i>
<b>On-Treatment</b>						
Number of Event (%)	10 (5.8)	14 (8.0)	9 (5.3)	15 (8.7)	19 (5.5)	29 (8.4)
Hazard ratio (95%CI)	0.72 (0.32, 1.62)	--	0.59 (0.26, 1.36)	--	0.65 (0.37, 1.16)	--
Log-rank p-value <sup>b</sup>	0.422	--	0.216	--	0.149	--
<b>Vital Status at End of Study</b>						
Number of Event	14 (8.0)	20 (11.5)	18 (10.5)	17 (9.8)	32 (9.3)	37 (10.7)
Hazard ratio (95%CI)	0.66 (0.33, 1.30)	--	1.08 (0.56, 2.09)	--	0.85 (0.53, 1.36)	--
Log-Rank p-value	0.228	--	0.825	--	0.489	--

Table 2. Survival Analysis on Fatal Adverse Event (Deaths + Lung Transplantations)

	<i>Study 004</i>		<i>Study 006</i>		<i>Pooled Study 004/006</i>	
	<i>Pirfenidone (N=174)</i>	<i>Placebo (N=174)</i>	<i>Pirfenidone (N=171)</i>	<i>Placebo (n=173)</i>	<i>Pirfenidone (N=345)</i>	<i>Placebo (n=347)</i>
<b>On-Treatment</b>						
Number of Event (%)	13 (7.5)	19 (10.9)	11 (6.4)	20 (11.6)	24 (7.0)	39 (11.2)
Hazard ratio (95%CI)	0.67 (0.33, 1.36)	--	0.55 (0.26, 1.14)	--	0.61 (0.36, 1.01)	--
Log-rank p-value <sup>b</sup>	0.267	--	0.106	--	0.054	--
<b>Vital Status at End of Study</b>						
Number of Event	17 (9.8)	24 (13.8)	22 (12.9)	22 (12.7)	39 (11.3)	46 (13.3)
Hazard ratio (95%CI)	0.66 (0.35, 1.23)	--	1.00 (0.56, 1.81)	--	0.82 (0.54, 1.26)	--
Log-Rank p-value <sup>d</sup>	0.188	--	0.992	--	0.362	--

Table 3. Survival Analysis on IPF Related Death

	<i>Study 004</i>		<i>Study 006</i>		<i>Pooled Study 004/006</i>	
	<i>Pirfenidone (N=174)</i>	<i>Placebo (N=174)</i>	<i>Pirfenidone (N=171)</i>	<i>Placebo (n=173)</i>	<i>Pirfenidone (N=345)</i>	<i>Placebo (n=347)</i>
<b><i>On-Treatment</i></b>						
Number of Event (%)	5 (2.9)	11 (6.3)	7 (4.1)	14 (8.1)	12 (3.5)	25 (7.2)
Hazard ratio (95%CI)	0.46 (0.16, 1.32)	--	0.49 (0.20, 1.23)	--	0.48 (0.24, 0.95)	--
Log-rank p-value <sup>b</sup>	0.147	--	0.128	--	0.036	--
<b><i>Vital Status at End of Study</i></b>						
Number of Event (%)	8 (4.6)	15 (8.6)	14 (8.2)	15 (8.7)	22 (6.4)	30 (8.6)
Hazard ratio (95%CI)	0.50 (0.21, 1.17)	--	0.95 (0.46, 1.97)	--	0.72 (0.41, 1.25)	--
Log-rank p-value <sup>b</sup>	0.111	--	0.894	--	0.239	--

Please submit the requested information as soon as possible or by COB, February 8, 2010. If you have any questions, please contact Eunice Chung, Regulatory Project Manager, at 301-796-4006.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22535	ORIG-1	INTERMUNE INC	PIRFENIDONE CAPSULE

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EUNICE H CHUNG  
02/04/2010

Your submission dated November 4, 2009, to NDA 22-535, is currently under review. We have the following requests for information:

1. Submit the narratives (or provide the location within the NDA) for the treatment-emergent deaths for all patients who were treated with placebo in both trials PIPF-004 and -006 (as listed in Table 5-37 in the Integrated Summary of Safety).
2. Clarify the manner in which cause of death was determined for all treatment-emergent deaths (as listed in Table 5-37, ISS). Specifically, provide clarification as to how a death was determined to be IPF-related.

Please submit the requested information as soon as possible or by COB, February 5, 2010. If you have any questions, please contact Eunice Chung, Regulatory Project Manager, at 301-796-4006.

Drafted by: BKarimi Shah/3FEB2010  
Initialed by: SSeymour/3FEB2010  
SBarnes/3FEB2010

Finalized by: Echung/3FEB2010

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22535	ORIG-1	INTERMUNE INC	PIRFENIDONE CAPSULE

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EUNICE H CHUNG  
02/03/2010

**MEMORANDUM OF TELECONFERENCE (Internal use only)**

**MEETING DATE:** January 29, 2010  
**APPLICATION:** 22-535  
**DRUG NAME:** Pirfenidone

**FDA ATTENDEES:**

Elizabeth Shang, Ph.D., Clinical Pharmacology Reviewer  
Yun Xu, Ph.D., Acting Clinical Pharmacology Team Leader  
Sally Seymour, M.D. Deputy Director for Safety  
Banu Karimi Shah, M.D. Clinical Reviewer

**BACKGROUND:**

The clinical pharmacology team wished to discuss with the sponsor over teleconference regarding recent responses to information requests and outstanding information requests.

**DECISIONS (AGREEMENTS) REACHED:**

The sponsor and the clinical pharmacology team agreed on the following timelines:

The reports and datasets for the drug-drug interaction studies, hepatic impairment studies and renal impairment studies as well as the urine volume data will be submitted by February 8, 2010.

For study PIPF-005, the PK parameter estimates in SAS transport files and summary statistics of all parameters (AUC and other parameters) as well as the complete urine dataset (urine amount, concentration, and volume) datasets will be submitted by February 19, 2010.

The full non-compartment analysis report for PIPF-005 will be submitted by March 15, 2010.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22535	ORIG-1	INTERMUNE INC	PIRFENIDONE CAPSULE

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EUNICE H CHUNG  
02/03/2010

Your submission dated November 4, 2009, to NDA 22-535, is currently under review. We have the following request for information:

1. Despite our attempt to reproduce the Progression-Free Survival event data ADTTE.XPT for Study 004, which was done by creating event data from ADEEF.XPT and applying your SAS code U004TTE.PDF, we were not able to replicate your results.

From ADTTE.XPT when tested='TTPFDTHR', the results are as follows:

# of Event = (b) (4) (PIPFHIGH) and (b) (4) (PLACEBO)

These numbers match with what was reported in the study report. However, recreation of your event data yielded different event rates. Please see the attached SAS code for the following rates:

# of Event = (b) (4) (PIPFHIGH) and (b) (4) (PLACEBO)  
HR= (b) (4)

Please clarify how you created the ADTTE.XPT data and explain the discrepancy.

Please submit the requested information as soon as possible or by COB, February 3, 2010. This response must also be submitted to the NDA as well. If you have any questions, please contact Eunice Chung, Regulatory Project Manager, at 301-796-4006.

6 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22535	ORIG-1	INTERMUNE INC	PIRFENIDONE CAPSULE

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/s/

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EUNICE H CHUNG  
01/29/2010

Your submission dated November 4, 2009, to NDA 22-535, is currently under review. We have the following requests for information:

1. Perform a subgroup analysis in both trials PIPF-004 and -006 using the pre-specified primary efficacy model (rank ANCOVA) and imputation methods for each of the subgroups listed below. In addition, provide demographic and baseline characteristics for each subgroup.
  - a) Patients who were previously enrolled in the INSPIRE trial
  - b) Patients who were not enrolled in the INSPIRE trial
2. The Agency's statistical reviewer produced the following table. Please verify the results. In addition, provide the SAS program and output. (Note: "Treatment period + F/U denotes the entire study period).

**Table 13. Survival Analysis on Fatal Adverse Event (Deaths + Lung Transplants)**

	<b>Pirfenidone 2403</b>	<b>Placebo</b>	
<b>Fatal Adverse Event</b>	<b>N of Event <sup>a</sup> (%)</b>	<b>N of Event <sup>a</sup> (%)</b>	<b>Hazard Ratio <sup>c</sup> (95% CI) p-value <sup>b</sup></b>
<b>Study 004</b>			
<i>N of Randomized</i>	174	174	--
<i>Treatment Period</i>	14 (11D+3L) (8.0)	21 (17D+4L) (12.1)	0.63 (0.32, 1.23), 0.174
<i>Treatment Period + F/U</i>	17 (14D+3L) (9.8)	24 (20D+4L) (13.8)	0.67 (0.36, 1.24), 0.201
<b>Study 006</b>			
<i>N of Randomized</i>	171	173	
<i>Treatment Period</i>	20 (16D+4L) (11.7)	22 (17D+5L) (12.7)	0.91 (0.49, 1.66), 0.745
<i>Treatment Period + F/U</i>	22 (18D+4L) (12.9)	22 (17D+5L) (12.7)	1.00 (0.55, 1.80), 0.984
<b>Combined Two Studies</b>			
<i>N of Randomized</i>	345	347	--
<i>Treatment Period</i>	34 (27D+7L) (9.9)	43 (34D+9L) (12.4)	0.77 (0.49, 1.20), 0.247
<i>Treatment Period + F/U</i>	39 (32D+7L) (11.3)	46 (37D+10L) (13.3)	0.82 (0.54, 1.26), 0.373

<sup>a</sup> Based on occurrence of event (death (D) or lung transplant (L)), or censoring in the absence of the event. Time to event was the event date minus randomization date plus one. The censoring date was the last available contact date, or the end of the treatment period (or treatment period + F/U).

<sup>b</sup> p-value was based on the log-rank test, stratified by geographic region (USA and ROW) comparing pirfenidone 2403 mg/d with placebo.

<sup>c</sup> Hazard ratio was based on the Cox proportional hazard model.

Please submit the requested information as soon as possible or by COB, Monday, February 1, 2010. This response must also be submitted to the NDA as well. If you have any questions, please contact Eunice Chung, Regulatory Project Manager, at 301-796-4006.

Drafted by: BKarimi-Shah/26JAN2010  
Initialed by: Feng Zhou/26JAN2010  
Joan Buenconsejo/27JAN2010  
SSeymour/26JAN2010  
SBarnes/27JAN2010

Finalized by: EChung/27JAN2010

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22535	ORIG-1	INTERMUNE INC	PIRFENIDONE CAPSULE

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/s/

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EUNICE H CHUNG  
01/27/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 22-535

**MEETING DENIED**

InterMune, Inc.  
3280 Bayshore Boulevard  
Brisbane, California 94005

Attention: Marianne Armstrong, Ph.D.  
Chief, Medical Affairs and Regulatory Officer, Senior Vice President

Dear Dr. Armstrong:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for pifrenidone capsules.

We also refer to your January 7, 2010, correspondence requesting a meeting to discuss the progress of the application review. We are denying the meeting because a meeting is not necessary at this time. We will provide feedback to the discussion points that you listed in your January 7, 2010, meeting request in a separate communication.

If you have any questions, call Eunice Chung at (301) 796-4006.

Sincerely,

*{See appended electronic signature page}*

Badrul A. Chowdhury, M.D., Ph.D.  
Director  
Division of Pulmonary and Allergy Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22535	GI-1	INTERMUNE INC	PIRFENIDONE CAPSULE

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/s/

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BADRUL A CHOWDHURY  
01/27/2010

Your submission dated January 12, 2010, to NDA 22-535, in response to our fax, dated January 6, 2010, is currently under review and we have the following requests.

1. For studies PAPF – 009, -010 and -11, submit descriptive statistics on the PK parameters listed below, a statistical summary of treatment comparisons, and datasets used for NCA analyses by January 26, 2010 in the most expedited method. The data files need to be in SAS transport files (.xpt format). In addition, provide associated data definition files.
  - a. Plasma PK parameters for pirfenidone and metabolite 5-carboxy-pirfenidone: C<sub>max</sub>, and t<sub>1/2</sub> (if permitted by the data), T<sub>max</sub>, AUC<sub>last</sub>, and metabolite-to-parent ratio by AUC, CL/F or CL (if permitted by the data)
  - b. Urinary PK parameters: CL<sub>r</sub>, Ae, and Ae%
2. We found deficiencies in the selection of PK endpoints in the study report for study PIPF 005. Provide descriptive statistics on the PK parameters listed below, a statistical summary of treatment comparisons, and datasets used for NCA analyses by January 26, 2010 in the most expedited method.
  - a. For single-dose cohort:
    - 1) Plasma PK parameters for pirfenidone and 5-carboxy-pirfenidone: C<sub>max</sub>, t<sub>1/2</sub> (as permitted by the data), T<sub>max</sub>, AUC<sub>last</sub>, and metabolite-to-parent ratio by AUC, CL/F or CL (if permitted by the data)
    - 2) Urinary PK parameters: CL<sub>r</sub>, Ae, and Ae%
  - b. For multiple-dose cohort:
    - a. Plasma PK parameters for pirfenidone and 5-carboxy-pirfenidone: C<sub>max</sub>, t<sub>1/2</sub> (as permitted by the data), T<sub>max</sub>, AUC<sub>last</sub>, and metabolite-to-parent ratio by AUC
    - b. Urinary PK parameters: CL<sub>r</sub>, Ae, and Ae%
3. For 1 and 2, consider handling concentrations below the limit of quantitation (BLQ) in the following way: Set all BLQ samples to zero. Provide comparison on parameter estimates between the method you originally used and the method we propose.
4. Provide a complete detailed PK report for PIPF-005 using NCA analysis including listings of tables and figures by February 16, 2010.

Please provide a response by the dates indicated above in the most expeditious method.  
The response will have to be submitted officially to the NDA as well.

---

Eunice Chung  
Regulatory Management Officer

Drafted by: YShang/January 21, 2010

Initialed by: Sbarnes/22JAN2010  
YXu/22JAN2010

Finalized by: Echung/22JAN2010

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22535	ORIG-1	INTERMUNE INC	PIRFENIDONE CAPSULE

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/s/

EUNICE H CHUNG  
01/22/2010



NDA 22-535

**FILING COMMUNICATION**

InterMune, Inc.  
3280 Bayshore Boulevard  
Brisbane, California 94005

Attention: Marianne Armstrong, Ph.D.  
Chief, Medical Affairs and Regulatory Officer, Senior Vice President

Dear Dr. Armstrong:

Please refer to your new drug application (NDA) dated November 4, 2009, received November 4, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Esbriet (pirfenidone 267 mg capsules).

We also refer to your submissions dated November 13 and 19, and December 3 and 30, 2009, and January 7, 2010.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is May 4, 2010.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by April 12, 2010.

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

Clinical:

1. Based upon preliminary review, you do not have replication of efficacy of pirfenidone for the treatment of idiopathic pulmonary fibrosis (IPF) to reduce decline in lung function. Of the two pivotal clinical trials, only PIPF-004 met the primary endpoint. The Shionogi clinical trial (SP3) cannot be used to support the efficacy of pirfenidone as the data were

not submitted for review. The adequacy of your application to support the efficacy of pirfenidone for the treatment of IPF will be a review issue.

2. [REDACTED] (b) (4) In your facsimile response, dated December 14, 2009 to our request for information, dated December 11, 2009, you stated that "SP3 only serves as supportive information in the InterMune NDA 22-535." Given that you have not provided the information requested, the Agency cannot review the patient level data from trial SP3. [REDACTED] (b) (4)

Nonclinical:

3. Our preliminary review identified that [REDACTED] (b) (4) and six (6) other potential impurities in the drug substance and drug product possess structural alerts. Exposure levels of either individual impurities or sums of structurally-related impurities may exceed the qualification threshold of 1.5 µg/day for genotoxic impurities (See Draft Guidance for Industry - Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches, December 2008). The Agency is conducting computational analyses for structure-activity relationships of mutagenicity for these impurities. Compounds that are positive in the analysis should be controlled at exposure levels not greater than 1.5 µg/day/patient. Those that are positive in the analysis and with exposure levels greater than 1.5 µg/day may require testing in the *in vitro* bacterial reverse mutation assay. Refer to ICH Q3A and Q3B guidance for qualification of non-genotoxic impurities. Qualification studies with a minimum duration of 90 days might be needed if levels are not in compliance with ICH Q3A and Q3B.

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

We also request that you submit the following information:

Chemistry, Manufacturing and Controls:

1. Provide a letter of authorization to review DMF [REDACTED] (b) (4) in support of your application.
2. Provide letters of authorization for all components of the container closure system used to package your drug product.
3. Provide the [REDACTED] (b) (4) of the proposed pirfenidone capsule.
4. Provide the observed levels of impurity [REDACTED] (b) (4) in the final drug substance.

5. Revise the limits for Total Impurities in the drug substance and drug product to reflect the data observed.

Labeling:

The following issues/deficiencies have been identified in your proposed labeling with regard to format. We request that you submit the revised labeling by January 22, 2010.

Highlights Section:

6. In the Contraindications Section, [REDACTED] (b) (4)
7. In the Adverse Reactions Section, add arthralgia as one of the adverse reactions with an incidence of >10%
8. In the Drug Interactions Section, consider the inclusion of practical instructions for the prevention of decreasing the likelihood of the interaction.
9. For the Revision date, remove the parentheses for the month/year.

Full Prescribing Information (FPI): Table of Contents

10. Remove periods after the numbers for the section and subsection headings.
11. Although the FDA-Approved Medication Guide should accompany the FPI at the end of the FPI, the medication guide should not be [REDACTED] (b) (4). Therefore, [REDACTED] (b) (4) should be omitted.

Full Prescribing Information :

12. The headings and sub headings should be in boldface font for Sections 1 Indications and Usage and 2 Dosage and Administration. Also, remove the periods after the numbers for these sections.
13. For Section 12.3 and Section [REDACTED] (b) (4), all non-heading and non-subheading words (i.e. Absorption, Distribution, Metabolism, Elimination, Geriatric, Gender, Obesity, Race, Hepatic, Renal Impairment, [REDACTED] (b) (4), and [REDACTED] (b) (4) and Tables and Figures must be normal font. Please change all italics and bold print to normal font.
14. In the Dosage and Administration Section, "TID" should be written out to "three times a day" or other variation.
15. Change "ULN" to "upper limit of normal" globally in the FPI.

16. Although the FDA-Approved Medication Guide should accompany the FPI at the end of the FPI, the medication guide should not be [REDACTED] (b) (4)  
[REDACTED] Therefore, [REDACTED] (b) (4)

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

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

### **REQUIRED PEDIATRIC ASSESSMENTS**

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

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

If you have any questions, call Eunice Chung, Regulatory Management Officer, at (301) 796-4006.

Sincerely,

*{See appended electronic signature page}*

Badrul A. Chowdhury, M.D., Ph.D.  
Director  
Division of Pulmonary and Allergy Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22535	ORIG-1	INTERMUNE INC	PIRFENIDONE CAPSULE

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/s/

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LYDIA I GILBERT MCCLAIN  
01/15/2010  
Signed for Dr. Badrul Chowdhury

Your submission dated November 4, 2009, to NDA 22-535, is currently under review. We have the following requests for information:

1. Submit the following data (or provide location within the NDA submission) for trials PIPF-004 and PIPF-006:
  - a. The number of patients in each treatment group who were listed for lung transplantation during the study period.
  - b. The patient identification number for each patient who was listed for lung transplantation during the study period.

We request your response by COB January 15, 2010 in the most expeditious method. The response will also have to be submitted officially to the NDA. If you have any questions, please contact Eunice Chung, Regulatory Project Manager, at 301-796-4006.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22535	ORIG-1	INTERMUNE INC	PIRFENIDONE CAPSULE

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/s/

EUNICE H CHUNG  
01/11/2010

Your submission dated November 4, 2009, to NDA 22-535, is currently under review and we have the following requests for information:

1. Reports

- a. Provide study reports of Studies PCLN-PIRF-114 and PCLN-PIRF-113
- b. Provide bioanalytical reports for Studies PIPF-007 and PIPF-004

2. Data sets for PK analysis

- a. Provide data files used for compartmental analyses on PIPF-009, PIPF-010, and PIPF-011. The data file should contain but not be limited to pirfenidone dosing record, pirfenidone and 5-carboxy-pirfenidone concentrations, and subject demographic and disease characteristic data. The data files need to be in SAS transport files (.xpt format). Provide associated data definition files.
- b. Provide the data file that contained subject demographic and disease characteristic record used for population PK analysis supporting the labeling statement. These information are missing in the submitted data files (ppkpool.xpt, pkallFp1.csv, pkallFp2.csv, pkallFp3.csv, pkallFp4.csv, pkallFp5.csv). The data files need to be in SAS transport files (.xpt format). Provide associated data definition files.
- c. Provide control stream and schematic of base structural model used for compartmental analysis on PIPF-005. Provide data file that contains subject demographic, disease characteristic record (e.g. albumin, CRCLN levels), adverse events and any other covariates used for compartmental analysis and labeling statement. The data files need to be in SAS transport files (.xpt format).

If further clarification is needed, the Agency is open to have a teleconference to discuss this. Please contact Eunice Chung at 301-796-4006.

Please provide a response by COB January 13, 2010 in the most expeditious method available. The response will also have to be submitted officially to the NDA.

---

Eunice Chung  
Regulatory Management Officer

Drafted by: Echung/January 6, 2010  
Initialed by: Sbarnes/January 6, 2010  
              EShang/January 6, 2010  
              PRoy/January 6, 2010

Finalized by: Echung/January 6, 2010

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22535	ORIG-1	INTERMUNE INC	PIRFENIDONE CAPSULE

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/s/

EUNICE H CHUNG  
01/06/2010



NDA 22-535

**PRIORITY REVIEW DESIGNATION**

InterMune, Inc.  
3280 Bayshore Boulevard  
Brisbane, California 94005

Attention: Marianne Armstrong, Ph.D.  
Chief, Medical Affairs and Regulatory Officer, Senior Vice President

Dear Dr. Armstrong:

Please refer to your new drug application (NDA) dated November 4, 2009, received November 4, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for pirfenidone capsules (267mg).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is May 4, 2010.

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 April 12, 2010.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before January 17, 2010.

If you have any questions, call Eunice H. Chung, Regulatory Management Officer at (301) 796-4006.

Sincerely,

*{See appended electronic signature page}*

Badrul A. Chowdhury, M.D., Ph.D.  
Director  
Division of Pulmonary and Allergy Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22535	ORIG-1	INTERMUNE INC	PIRFENIDONE CAPSULE

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/s/

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BADRUL A CHOWDHURY  
12/29/2009

Your submission dated November 4, 2009, to NDA 22-535, is currently under review and we have the following requests:

Please provide:

1. SAS Macro program called "%SSIMPUTE" which was used in the SAS program (u004adef.pdf) for the imputation.
2. All the efficacy (include the mortality) data sets, programs that were used for the interim analyses, and interim analysis reports.

Please provide a response by COB December 28, 2009, in the most expedited method. The response will have to be submitted officially to the NDA as well.

---

Eunice Chung  
Regulatory Management Officer

Drafted by: EChung/December 17, 2009

Initialed by: Sbarnes/December 17, 2009  
FZhou/December 17, 2009  
TPermutt/December 17, 2009

Finalized by: Echung/December 18, 2009

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22535	ORIG-1	INTERMUNE INC	PIRFENIDONE CAPSULE

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/s/

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EUNICE H CHUNG  
12/18/2009

Your submission dated November 4, 2009, to NDA 22-535, is currently under review and we have the following requests:

1. Conduct a non-compartmental analysis and provide related pharmacokinetic summary reports including listings of tables and figures on the following clinical pharmacology studies:
  - a. PIPF-009 renal impairment study
  - b. PIPF-010 drug-drug interaction study
  - c. PIPF-011 hepatic impairment study
2. Provide a pharmacokinetic summary report of non-compartmental analysis and full pharmacokinetic report of compartmental analysis on study PIPF-005:
  - a. The pharmacokinetics of oral pirfenidone in healthy older adults, including effects of multiple-dosing, dose-ranging, food, and antacids.

Please provide a response by COB January 4, 2010 in the most expedited method. The response will have to be submitted officially to the NDA as well.

---

Eunice Chung  
Regulatory Management Officer

Drafted by: YShang/December 16, 2009

Initialed by: Sbarnes/December 16, 2009  
PRoy/December 16, 2009

Finalized by: Echung/December 16, 2009

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22535	ORIG-1	INTERMUNE INC	PIRFENIDONE CAPSULE

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/s/

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EUNICE H CHUNG  
12/16/2009

Your submission dated November 4, 2009, to NDA 22-535, is currently under review. We have the following requests for information:

Please submit the following data for study SP3:

- 1) Case report forms for all deaths, serious adverse events, or adverse events leading to discontinuation
- 2) Narratives for all deaths
- 3) The SAS data sets in the same format and with the same variables which you have provided for studies PIPF-004 and PIPF-006
  - a) Please include tabulations and analysis data sets, which were used to create the analysis data sets from the tabulations, as well as all efficacy analyses programs with usage guide documents (like table-program-guide.pdf in PIPF-004).

Please submit the requested information by COB, Friday, December 18, 2009. If you have any questions, please contact Eunice Chung, Regulatory Project Manager, at 301-796-4006.

Drafted by: EChung/11DEC2009

Initialed by: SBarnes/11DEC2009  
SSeymour//11DEC2009  
FZhou//11DEC2009  
TPermutt/11DEC2009

Finalized by: EChung/11DEC2009

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22535	ORIG-1	INTERMUNE INC	PIRFENIDONE CAPSULE

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/s/

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EUNICE H CHUNG  
12/11/2009



NDA 22-535

**NDA ACKNOWLEDGMENT**

InterMune, Inc.  
3280 Bayshore Blvd.  
Brisbane CA 94005

Attention: Marianne Armstrong, Ph.D.  
Chief, Medical Affairs and Regulatory Officer, Senior Vice President

Dear Dr. Armstrong:

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: pirfenidone capsules 267mg

Date of Application: November 4, 2009

Date of Receipt: November 4, 2009

Our Reference Number: NDA 22-535

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 January 3, 2010 in accordance with 21 CFR 314.101(a).

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

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Pulmonary and Allergy Products  
5901-B Ammendale Road

Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size.

Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>

If you have any questions, call Eunice Chung, Regulatory Management Officer, at (301) 796-4006.

Sincerely,

*{See appended electronic signature page}*

Sandy Barnes  
Chief, Project Management Staff  
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Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22535	ORIG-1	INTERMUNE INC	PIRFENIDONE CAPSULE

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/s/

EUNICE H CHUNG on behalf of SANDRA L BARNES  
11/18/2009



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

**Meeting Type:** B  
**Meeting Category:** Pre-NDA  
**Meeting Date and Time:** September 17, 2008 @ 3:00  
**Meeting Location:** White Oak  
**Application Number:** 67,284  
**Product Name:** Pirfenidone  
**Received Briefing Package**  
**Sponsor Name:** InterMune  
**Meeting Requestor:** Mike Johnston  
**Meeting Chair:** Badrul Chowdhury, M.D., Ph.D.  
**Meeting Recorder:** Ladan Jafari  
**Meeting Attendees:**

**FDA Attendees:**

Banu Karimi-Shah, M.D., Medical Reviewer  
Sally Seymour, M.D., Medical Team Leader  
Ted Guo, Biometrics Reviewer  
Sandra Suarez, Ph.D., Clinical Pharmacology Reviewer  
Wei Qiu, Ph.D., Clinical Pharmacology Team Leader (Acting)  
Badrul Chowdhury, M.D., Ph.D., Director  
Ladan Jafari, Regulatory Health Project Manager

**Sponsor Attendees:**

**InterMune Participants:**

Steve Ammons, PhD; Vice President Preclinical Research/Development  
Marianne Armstrong, PhD; Chief Medical Affairs and Regulatory Officer  
Bill Bradford, MD, PhD; Senior Vice President, Clinical Science and Biometrics  
Spencer Hudson, PhD; Vice President, Biometrics  
David Kardatzke, PhD; Associate Director, Biometrics  
Steve Porter, MD, PhD; Chief Medical Officer  
Radha Radhakrishnan, PhD; Senior Director Process Development

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 <sup>(b) (4)</sup> Consultant, Pharmacology/Biopharmaceutics  
Sasan Sabrdaran, MD; Director, Drug Safety Risk Management  
Isa Samuels, Senior Manager, Regulatory Affairs  
Javier Szwarcberg, MD, MPH, Senior Director, Clinical Science

InterMune submitted a meeting request dated April 25, 2008, to discuss the submission of an NDA for pirfenidone. InterMune also submitted a briefing package dated August 7, 2008, which contained a list of questions to be discussed at this meeting. Upon review of the briefing package, the Division responded to InterMune's questions via FAX on September 15, 2008. The content of that FAX is printed below. All discussion items are printed directly after each FDA response. InterMune's questions are in bold; FDA's responses are in *Italics*; discussions are in normal font.

**1. Does the FDA agree with the proposed plan for submission of information as suggested in the 24 April 2008 “Request for Submission of Portions of an Application”?**

**Response:**

*The proposed schedule for submission of portions of your NDA application is at your discretion.*

**2. Does the FDA agree with proposed structure of the eCTD NDA?**

**Response:**

*The proposed structure of the eCTD NDA is acceptable.*

**3. Does the FDA agree with the proposed table of contents for the NDA?**

**Response:**

*The proposed table of contents appears acceptable.*

**4. For both the NDA submission and the 120-day Safety Update, InterMune plans to submit electronic bookmarked and hyperlinked case report forms (CRFs). (The specific CRFs proposed for submission are noted under Question 7 and Question 8, below.) Does the FDA agree with using the electronic format proposed for submission of these CRFs?**

**Response:**

*We agree.*

**5. This question pertains to the labeling. InterMune requested that this question be removed at this time.**

**6. Does the FDA agree that the number of patients to be included in the safety database is adequate to support submission of the marketing application?**

**Response:**

*The proposed safety database appears to be adequate to support submission of the marketing application.*

**7. Does the FDA agree with the proposed plans for submission of CRFs and patient narratives for the NDA?**

**Response:**

*We agree with the proposed plan.*

**8. Does the FDA agree with the proposed plans for the 120-day safety update?**

**Response:**

*We agree.*

**9. InterMune proposes to include the final CSRs for the Marnac-sponsored studies (PIPF-001, PIPF-003, and IPP/Extension Studies) in the NDA. These studies will not be summarized or integrated into the NDA. Does the FDA agree that a waiver is appropriate for these three clinical study reports?**

**Response:**

*While we agree that the three clinical study reports should not be integrated into the ISE and ISS, include a brief summary of the safety findings from each of these studies in your submission.*

**Discussion:**

InterMune indicated that although they would not be integrating the Marnac-sponsored studies into the ISS and ISE, they would include a brief summary of the safety findings from these studies in the ISS in addition to the clinical study reports in module 5.

**10. InterMune believes that all outstanding issues have been addressed concerning the clinical program for pirfenidone. Does the FDA agree?**

**Response:**

*We agree that your application proposes to address issues that have been raised in previous communications with the Agency, however whether the data submitted will adequately address all outstanding issues will be a review issue. See additional clinical comments below as well as the response to Question 19 (Clinical Pharmacology).*

*We also have the following additional clinical comments*

*We remind you of the Division's stance in the End-of-Phase 2 (EOP2) meeting in which we stated that mortality is the ideal primary endpoint in a study of IPF treatment. You have proposed forced vital capacity (FVC) as the primary outcome in your pivotal efficacy studies, which is not an established surrogate for mortality in this patient population. Further, we remain uncertain as to what would constitute a clinically meaningful outcome based on FVC. As you have chosen to proceed with a clinical development program in which mortality is not the primary endpoint, we remind you that the efficacy of pirfenidone will not be based solely upon "winning" on the primary endpoint of change in FVC. We will look at the totality of the data and what drives the primary endpoint. It is imperative that the secondary endpoints, many of which are those that are clinically meaningful to patients, support the primary endpoint and the efficacy of pirfenidone in IPF patients.*

*In section 11.5 of the briefing package, you state your plans to submit an Integrated Summary of Efficacy (ISE) in the NDA which conforms to the Guidance for Industry published in 1988. We refer you to the August 2008 Draft Guidance for Industry – Integrated Summary of Effectiveness.*

*Clarify that data collected from the low-dose group (1197 mg/day) in study PIPF-004 will be included in the ISS and ISE.*

**Discussion:**

InterMune indicated that they will pool the data for both the low and high doses in the ISS. For the ISE, however, the data will not be pooled, as the low dose (1197/mg/day) was evaluated in only one study (PIPF-004). The ISE will include a discussion of dose comparability and a summary of the PK/PD relationships, a full analysis of which will be included in the clinical study reports.

*Clarify that your ISS will include an outlier analysis of abnormal laboratory values and ECG parameters.*

**Discussion:**

InterMune clarified that an outlier analysis of abnormal laboratories and ECG parameters would be included in the ISS. Specifically, the ISS would include a summary of outliers with QTc intervals > 500 ms.

**11. Does the FDA agree with the proposed amended statistical analysis plan for the pivotal studies (PIPF-004 and PIPF-006)?**

**Response:**

*Your revised statistical analysis plan will be reviewed when we receive your NDA submission.*

**12. Does the FDA agree with the proposed statistical analysis plan for the pooled analyses in the Integrated Summary of Safety (ISS) to be included in the NDA submission?**

**Response:**

*Refer to our “additional clinical comments” above.*

**13. Does the FDA agree with the proposed statistical analysis plan for the pooled analyses in the Integrated Summary of Efficacy (ISE), that is, with pooling data from the pivotal studies PIPF-004 and PIPF-006 as well as presenting data from each study?**

**Response:**

*We refer you to the newly published “Guidance for Industry - Integrated Summary of Effectiveness” dated August 2008.*

**Discussion:**

- InterMune asked if they would receive any more feedback from the Division with regard to their statistical analysis plan.
  - The Division stated that we do not anticipate sending any other comments until the NDA is received.

**14. Does FDA agree with InterMune’s proposal to submit case report tabulations in CDISC SDTM version 3.2 format, accompanied by a define.xml metadata file for those studies identified below? For all other studies, SAS datasets will be submitted in the traditional “listing dataset” format with a define.pdf metadata file. Planned CDISC-formatted studies to be included in the NDA are as follows:**

- PIPF-004, a Phase 3 safety and efficacy study
- PIPF-006, a Phase 3 safety and efficacy study
- PIPF-002 (interim report), a Phase 2 long-term safety study
- PIPF-009, a Phase 1 renal impairment study
- PIPF-010, a Phase 1 drug interaction study

- **PIPF-011, a Phase 1 hepatic impairment study**
- **ISS**
- **ISE**

**Response:**

*We do not have any comments at this time.*

**Discussion:**

- InterMune asked if they could submit the major study reports on CDISC.
  - The Division agreed with the proposal.

**15. Does the FDA agree with InterMune's plans for the population pharmacokinetic (PK) and pharmacokinetic-pharmacodynamic (PK-PD) analyses as detailed in the PK and PK-PD data analysis plan?**

**Response:**

*We agree with your proposal. The proposed population PK and PK-PD plans are acceptable.*

**16. Does the FDA agree with InterMune's plans for the format of the datasets that support the population PK and PK-PD analyses as detailed in the population PK and PK-PD data analysis plan?**

**Response:**

*The proposed format of the datasets (.XPT and .CSV) in support of the population PK and PK-PD are acceptable. We have the following suggestions regarding the format of the data.*

- *Provide a description of each data item in a Define.pdf file. Flag and maintain any concentrations and/or subjects that have been excluded from the analysis in the datasets.*

**Discussion:**

- InterMune indicated that they used a new software where a quality control process is in place and any outliers are pooled and identified. InterMune asked if the Division agreed with this proposal.
  - The Division asked that InterMune also submit the original dataset, including outliers and non-outliers.

- *Provide model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submit these files as ASCII text files with \*.txt extension (e.g.: myfile\_ctl.txt, myfile\_out.txt).*
- *Provide a model development decision tree and/or table which gives an overview of modeling steps.*
- *For the population analysis reports we request that you submit individual plots for a representative number of subjects in addition to the standard model diagnostic plots. Include observed concentrations, the individual prediction line and the population prediction line in each individual plot. . Include model parameter names and units, in the report, tables. . For example, present oral clearance as CL/F (L/h) and not as THETA(1), etc. Also provide a description of the clinical application of modeling results in the summary of the report.*

**Discussion:**

- InterMune inquired if the Division could clarify as to how many individual plots they would need for the above request.
  - The Division indicated that 10-20% is reasonable.

**17. InterMune has identified the following three outstanding items concerning the biopharmaceutics program and is seeking the FDA's concurrence with InterMune's positions regarding these items.**

- a. Studies that test the potential for pirfenidone to inhibit or induce cytochrome P450 (CYP) metabolism** (b) (4)
- b. A mass balance study is not needed**
- c. A single-dose renal insufficiency study is adequate.**

**a. Based on the results of the nonclinical and clinical studies, does the FDA agree?**

**Response:**

- a. (b) (4)  
The in vivo testing of the potential for pirfenidone to inhibit CYP metabolism is warranted if estimated  $[I]/K_i$  ratios are greater than 0.1 for all major CYP P450 enzymes. You also need to examine whether pirfenidone is a mechanism-based inhibitor by conducting an in vitro time-dependent inhibition study.

(b) (4)  
. *The in vivo testing of the potential for pirfenidone to induce CYP metabolism is warranted unless in vitro studies indicate that pirfenidone does not induce CYP1A2 or CYP3A metabolism (e.g. fold change that is more than 40% of the positive control can be considered as an enzyme inducer) (refer to guidance for industry: Drug Interaction Studies-Study Design, Data Analysis, and Implications for Dosing and Labeling).*

**Discussion:**

- InterMune indicated that the response above contradicts that obtained in December 2006. InterMune asked if the Division could clarify if in-vivo studies are needed.
  - The Division reiterated that in vivo testing of the potential for pirfenidone to inhibit CYP metabolism is warranted if estimated [I]/Ki ratios are greater than 0.1 for all major CYP P450 enzymes.
- InterMune stated that preliminary results indicate [I]/Ki ratios of about 0.2 for some enzymes. However, they would repeat the study due to limitations encountered in the previous in vitro studies.
  - The Division stated that if data show that in-vivo study is needed, ([I]/Ki ratios >0.1), then study results must be submitted in the NDA.

**b. Based on the results of the nonclinical and clinical studies, which were submitted to the IND, does the FDA agree that a mass balance study is not needed?**

**Response:**

*Given the high urine recovery of pirfenidone and its metabolites (i.e., 80–84%), we agree that a mass balance study is not needed. However, you need to address the issue of unique metabolites in your NDA submission. The in vitro drug metabolism and preclinical data can be provided as supportive data.*

**c. Does the FDA agree with the adequacy of a single-dose renal insufficiency study?**

**Response:**

(b) (4)  
. *Therefore, we can not make a decision about the need for a multiple dose renal insufficiency study at this time. We request that you analyze the pharmacokinetic data from Phase 1 studies using non-compartmental analysis. If the non-compartmental analysis results demonstrate that pirfenidone follows linear and time-independent pharmacokinetics, then a multiple renal insufficiency study is not warranted.*

**Discussion:**

- InterMune stated that [REDACTED] (b) (4)  
[REDACTED]
- The Division reiterated that if InterMune's model and data suggest that pirfenidone follows non-linear and time-dependent pharmacokinetics, then a multiple dose renal insufficiency study is warranted. The Division suggested that InterMune provide both compartmental and non-compartmental analysis results. If InterMune believes that multiple dose administration is not necessary for the renal impairment study and other phase 1 studies (such as hepatic impairment, DDI), they should provide their rationale in the NDA submission.

**18. InterMune believes that ICH Guideline E14 on the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs has been adequately fulfilled by performing Study PIPF-007. Does the FDA agree?**

**Response:**

*The clinical evaluation of the QT/QTc prolongation program is under review. We will respond to this question at a later date.*

**19. InterMune believes that all outstanding issues have been addressed concerning the clinical pharmacology and biopharmaceutics programs. Does the FDA agree?**

**Response:**

- *Evaluate the potential for pirfenidone to act as a substrate/inhibitor/ or inducer of P-gp transporter.*

**Discussion:**

- InterMune indicated that they would do an in-vitro study to evaluate the potential for pirfenidone to act as a substrate/inhibitor/or inducer of P-gp transporter.
- *Determine the effect of dialysis on the PK of pirfenidone and its major metabolite, 5-carboxy-pirfenidone, for dosage adjustment.*

**Discussion:**

- InterMune indicated that a study in patients with IPF who are on dialysis is not easily done. InterMune asked if it is acceptable not to do such a study.
  - The Division stated that the NDA should include a rationale for not doing such a study.
- InterMune asked if that would be a labeling issue. InterMune also asked if that would be a filing issue.
  - The Division stated that it is premature to discuss labeling at this time. The Division also stated that this would not be a filing issue.
- *Calculate and report pharmacokinetics parameters using non-compartmental analysis.*
- *As we stated in response to question 17c, it is not clear if pirfenidone follows linear pharmacokinetics within the range of therapeutic doses. If the PK of pirfenidone is nonlinear or time-dependent based on non-compartmental analysis, determine the effect of hepatic impairment and the effect of concomitant medications after multiple dose administration of pirfenidone.*

**20. InterMune believes that all outstanding issues have been addressed concerning the nonclinical program. Does the FDA agree?**

**Response:**

*The lists of nonclinical studies in Section 15 appear generally adequate to support filing of an NDA. However, you should address any issues of unique or disproportionate metabolites in humans as compared to nonclinical test species (see Guidance for Industry Safety Testing of Drug Metabolites February 2008) in the NDA.*

**21. InterMune will be qualifying an alternative drug substance manufacturing site. Does the FDA (a) agree with InterMune's approach and (b) agree that these data, if available at the time of NDA submission, are adequate to support inclusion of the second, alternative drug substance supplier in the marketing application?**

**Response:**

*The proposal is acceptable.*

**22. Does the FDA agree that the extent of drug substance and drug product stability data is adequate to support submission of the marketing application?**

**Response:**

*The proposal is acceptable. Sufficient stability data must be available at the time of filing to support the proposed expiration date. If the NDA is accepted as a priority review there may not be sufficient time to assess additional information submitted after the original submission. The proposed 9 months of data for the blister presentations will be evaluated in terms of the available over-all data.*

**23. InterMune is proposing to submit one representative executed drug product batch record that was used for primary stability in the NDA. Does the FDA agree with this approach?**

**Response:**

*The proposal is acceptable.*

**24. InterMune is proposing to request a Categorical Exclusion for an Environmental Analysis per 21 CFR 25.31(b). Does the FDA agree with this approach?**

**Response:**

*The proposal is acceptable.*

**25. InterMune believes that there are no additional requirements for completing the Quality module of the NDA. Does FDA agree?**

**Response:**

*In general there are no additional requirements. We request that you include the following additional information in the NDA:*

- a. Provide in-house specifications, including testing and acceptance criteria, for the drug substance and the excipients, including information to demonstrate that residual solvents in the excipients are adequately controlled.*
- b. Provide references to the appropriate Food Additive Regulations for the materials of construction in the packaging materials.*
- c. Provide the qualitative and quantitative composition and dissolution profiles for formulations used in all studies including those listed in Table 12-1 (pages 70 and 71 of your meeting package).*

**General Discussions:**

The Division inquired as to the status of the pivotal studies. InterMune responded that they are planning to close all the studies in October 2008. The Division asked if there has been any interim looks at the data or if there has been any suggestions from the DSMB. InterMune responded that the DSMB have recommended that they continue with the study.

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Drafted by: LJ/9-19-08

Initialed by: Suarez/9-26-08  
Qiu/9-26-08  
Karimi-Shah/9-23-08  
Seymour/9-23-08  
Chowdhury/9-25-08

Filename: I67284mtgmin.doc

Linked Applications

Sponsor Name

Drug Name

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IND 67284

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INTERMUNE INC

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PIRFENIDONE

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/s/  
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LADAN G JAFARI

09/29/2008

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** December 14, 2004  
**TIME:** 12:30 PM  
**LOCATION:** Parklawn, Conference Room 17-05  
**APPLICATION:** IND# 67,284 Pirfenidone

### **Representatives of FDA**

Badrul A. Chowdhury, M.D., Ph.D., Division Director  
Diane Centeno-Deshields, R.Ph., Division of Orphan Drug Products  
Timothy Robison, Ph.D., Pharmacologist  
Sally Seymour, M.D., Medical Officer  
Joseph Sun, Ph.D., Pharmacology Team Leader  
Eugene Sullivan, M.D., Deputy Division Director  
Sue Jane Wang, Ph.D., Biostatistics, Acting Team Leader  
Anthony Zeccola, Regulatory Management Officer

### **Representatives of Intermune**

William Bradford, M.D., Ph.D., Vice President, Clinical Science  
Karen Chen, Senior Associate, Regulatory Affairs  
Ellen Cheung, Ph.D., Senior Director, Preclinical Research  
(b) (4) Clinical Pharmacology Consultant  
Michael Johnston, Director, Regulatory Affairs  
David Kardatzke, Ph.D., Associate Director, Biometrics  
Russell Kawahata, Ph.D., Vice President, Technical Operations  
Jeffery Loutit, M.D., Senior Director, Clinical Science  
(b) (4)  
Steven Porter, M.D., Ph.D., Senior Vice President, Clinical Affairs  
(b) (4) Toxicology Consultant  
Susan Vermaer, Vice President, Regulatory Affairs

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**Background:** End of Phase 2 meeting for Intermune's IND 67, 284 for pirfenidone.

### **Discussion**

**Question 1: Does the Agency agree that adequate data are available to proceed with the Phase 3 registration study, PIPF-004?**

*DPADP Response: The completed Phase 2 studies have many limitations and therefore, do little to support the efficacy of pirfenidone for the treatment of IPF. The completed Phase 2 studies are hypothesis generating. Ideally, a Phase 2 program includes stronger preliminary evidence of efficacy and dose ranging information to support dose selection*

*for the confirmatory Phase 3 program. If you choose to proceed with the proposed Phase 3 study, you do so without an understanding of the dose response relationship and dosing interval of pirfenidone. Thus, your dose selection may be incorrect.*

*Intermune acknowledged these comments, but stated that they believe that they are ready to proceed to Phase 3, based on the available data.*

**Question 2a: Will a single, Phase 3 study in this serious and unmet orphan indication, if successful, be adequate to provide substantial evidence of safety and efficacy in an NDA filing?**

*DPADP Response: Data from this single study are unlikely to be sufficient for approval unless the results suggest an effect that is highly clinically and statistically persuasive. A decision regarding approval would need to take into account all of the findings of the study in the context of the Agency's Guidance for Industry – Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products ([www.fda.gov/cder/guidance/guidances/index.html](http://www.fda.gov/cder/guidance/guidances/index.html)).*

*All available data will be examined to either support or weaken reliance on a single trial.*

*Limitations of the current proposal include lack of knowledge of the specific mechanism of action of pirfenidone in IPF, lack of preliminary evidence of efficacy, and the lack of knowledge about the dose response relationship.*

*The addition of a second dose to the proposed study could provide further evidence for the efficacy and safety of pirfenidone.*

(b) (4)

*Intermune explained that they felt one study would be sufficient because they feel the endpoint is robust. Further, they felt that larger single study may be more likely to show benefit on various secondary efficacy endpoints than would two, smaller studies. Finally, Intermune stated that dose-ranging in a Phase 3 study may not be possible.*

**Question 2b: Does the Agency concur with the proposed primary endpoint?**

*DPADP Response: No. The Division must be certain the primary endpoint is clinically meaningful. The ideal primary endpoint for a study in IPF is mortality. If a study evaluating mortality is not feasible, alternative endpoints will be necessary. Surrogate endpoints for mortality in patients with IPF have not been established.*

*Your proposed primary endpoint is the time to death or to progression of disease (relative decline in the %predicted FVC of = 10% on 2 consecutive visits). You propose to use change in FVC (= 10%) as a surrogate for mortality. Despite your rationale, the*

*Division cannot conclude that the time to a relative decline in FVC of  $\geq 10\%$  is an established surrogate for mortality or that it is clinically meaningful. We must be confident the threshold selected represents unequivocal, clinically meaningful disease progression.*

*You could consider a definition of disease progression similar to the ATS criteria for “failure to respond to therapy” for IPF. For example, disease progression indicated by two or more of the following:*

- *A decrease in VC*
- *A decrease in DLCO*
- *A decrease in oxygen saturation or rise in A-aPO<sub>2</sub> at rest.*

*Am J Respir Crit Care Med 2000; Vol. 161, page 646-664*

*If you choose to proceed with the proposed primary endpoint, the efficacy of pirfenidone will not be based solely upon ‘winning’ on the primary endpoint. The Division will look at what “drives” the primary endpoint. A ‘win’ on the primary endpoint driven mostly by the decrease in FVC would be less compelling.*



The DPADP encouraged InterMune to submit the proposed protocol for review and comments prior to proceeding with the study.

**2c. (Biostatistics): The design of the proposed phase 3 study (PIPF-004) would provide > 90% power to detect a statistically significant treatment difference in the analysis of time to disease progression with the following assumptions:**

- **a pirfenidone-to-placebo hazard ratio of 0.6**
- **162 events estimated to occur during an 18-month enrollment period and 60-week treatment/follow-up period**
- **testing performed using a two-tailed, log-rank test at an overall 0.05 significance level (Section 10.7 and Appendix 3)**

**Are the statistical considerations for the proposed phase 3 study acceptable?**

*DPADP Response: Given the proposed primary efficacy endpoint of time to disease progression as defined in the protocol and if your assumptions are correct, the statistical consideration for the initial sample sizing planning stated above is acceptable. However, you also planned for possible sample size modification. Provide the algorithm with literature citation of the proposed sample size modification. For a complete assessment of the statistical analysis plan, please also provide the strategies to handle the missing data should it become informative. As discussed in Question 2b, should you change the*

*proposed primary efficacy endpoint with consideration of sample size reassessment, submit your proposal for further statistical review.*

**Question 2d: Are the other important components of the proposed Phase 3 study, such as dose selection, choice of secondary endpoints, frequency of safety and laboratory assessments, frequency of Data Monitoring Committee reviews and proposed interim analysis, acceptable?**

*DPADP Response: The Division is uncertain if the dose or dosing interval you have chosen for the proposed Phase 3 study is appropriate. The UCSD SOBQ has not been validated in the IPF population and if the data is intended for the product label, you should submit data establishing its validity in the population studies as well as data establishing the minimal clinically meaningful change. Frequency of safety assessments, laboratory assessments, and frequency of DMC reviews are acceptable.*

**Question 2e: Does the Agency recommend that InterMune proceed with a request for a Special Protocol Assessment of Protocol PIPF-004?**

*DPADP Response: No. The Division is unlikely to agree that the single proposed Phase 3 protocol will be sufficient for approval. As noted previously, you lack preliminary evidence of efficacy. In addition, the Division is uncertain if your dose selection is appropriate and does not agree with your selected primary endpoint. Finally, given the limited experience with drug development for this disease, a Special Protocol Assessment may not be wise.*

**Question 3: Would the Agency accept this safety database for registration given that the published estimated prevalence of IPF is approximately 13.2-20.2 per 100,000 people in the United States (Coultas 1994)?**

*DPADP response: You propose that the overall number of subjects exposed to pirfenidone will be >600. Assuming no important safety signals, the proposed safety database is acceptable. The Division expects that for registration of pirfenidone, an integrated summary of all available safety information of pirfenidone would be submitted with the NDA submission as specified in 21 CFR 314.50 (5) (vi) (a).*

InterMune indicated the safety database would include roughly 400 subjects on pirfenidone from phase 3 studies. DPADP stated that certain factors will be considered in determining the adequacy of the safety database. These include the indication, the demonstrated efficacy effect size, and any safety signals seen.

**Question 4 (clinical Pharmacology): Will the clinical pharmacology program as proposed be adequate to support filing of an NDA for this indication?**

*No.*

- *Conduct a mass balance study in humans (ADME) to investigate the disposition and routes of elimination following single intravenous and/or oral administration of the drug and to quantify and structurally characterize the major compound-related components in plasma and excreta (urine and faeces).*
- *Conduct appropriate drug-drug interaction studies based on the results of the in vitro metabolism studies.*
- *Be aware of the draft ICH Guidance for thorough QT study for NMEs (E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs - <http://www.fda.gov/cder/guidance/6378dft.htm>)*
- *Assess the pharmacokinetics of the drug and major metabolites in special populations such as: elderly, patients with hepatic and renal impairment (already planned).*
- *Link all formulations (capsules & tablets) used in the clinical development program by in vitro dissolution profile comparison.*

Question #5 (Preclinical)

**a. Are the data from the available nonclinical studies adequate to support initiation of the proposed Phase 3 clinical development program (Section 8)?**

*Available nonclinical studies are adequate to support the proposed Phase 3 clinical development program.*

**b. Will the proposed nonclinical program (existing and planned studies) be adequate to support a marketing application of pifedidone (section 8)?**

*i. The Segment II teratology study conducted in 1978 with rabbits that received pifedidone by the intramuscular route is considered inadequate as follows:*

*There was no evidence of maternal toxicity.*

*Individual external, visceral, and skeletal malformations and variations were not identified.*

*A Segment II teratology study with rabbits using the oral route should be provided with an NDA submission as noted above. Maternal toxicity should be demonstrated as described in ICH S5A.*

*ii. Characterizing the toxicological properties of pifedidone is essential for development and marketing. The identification of the dose-limiting toxicity and/or target organ(s) of toxicity is critical for its toxicity characterization. Target organs of toxicity were not identified in either the 6-month rat study or 9-month dog study.*

*A 1-month toxicology study using the intravenous route with dogs should be conducted for approval. Dose-limiting toxicity and/or target organ(s) of toxicity should be demonstrated in the study. This study would be expected to include a comprehensive histopathological examination of tissues and organs.*

**Question #6: Does the Agency agree that carcinogenicity studies need not be conducted for this indication?**

*The genotoxicity assays of the standard battery are intended as screening assays to assess potential interaction(s) with DNA (i.e., hazard identification). Negative results do not preclude the need for carcinogenicity studies.*

*Treatment of IPF [REDACTED] (b) (4) patients with pirfenidone will be chronic (i.e., =3 months).*

*According to ICH S1A:*

*For drugs with a chronic indication, carcinogenicity studies usually need to be completed before application for marketing approval.*

*For pharmaceuticals developed to treat certain serious diseases, carcinogenicity testing need not be conducted before market approval although these studies should be conducted post approval.*

*- In instance where the life-expectancy in the indicated population is short (i.e., less than 2 to 3 years), no long-term carcinogenicity studies may be required.*

*The median survival time for IPF patients ranges from 3 to 5 years. With improvements in treatment, it would be expected that survival time should increase.*

[REDACTED] (b) (4)

*Thus, carcinogenicity studies are required post-approval.*

*You are encouraged to consider a transgenic mouse carcinogenicity study in addition to the 2-year rat carcinogenicity study.*

**Question 7: Does the Agency agree that a waiver should be granted releasing InterMune from the requirement to study pirfenidone in a pediatric population?**

*Yes.*

**Question 8: Does the Agency foresee any additional data requirements at this time to enhance the Phase 3 IPF development program?**

*Information regarding the dose response relationship of pirfenidone in patients with IPF would add another layer of support to your Phase 3 development program.*

The following additional comments were conveyed to the Sponsor.

*Use of alternative treatments for IPF during the study may complicate interpretation of the study results.*

*Consider including endpoints related to acute exacerbations as secondary endpoints.*

*Because of the abnormal liver function tests noted in the Shionogi study, you should consider excluding subjects with liver disease.*

*Your Phase 3 studies should be conducted with the to-be-marketed formulation of pirfenidone.*

*From a preclinical standpoint, there are no additional data requirements for the Phase 3 program.*

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/s/

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Anthony Zeccola  
3/10/05 03:18:08 PM