

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208780Orig1s000**

**CHEMISTRY REVIEW(S)**

NDA-208780-ORIG-1 » Manufacturing Facility Inspection

## Overall Manufacturing Inspection Recommendation

under evaluation- CMS 137874

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### Inspection Management Form

As of Dec 13, 2016 4:43 pm GMT

Assigned To



**Cassandra Abellard**  
Consumer Safety Officer-  
OPF-DIA BII

[Edit Assignment](#)

This was done on  
**Oct 20, 2016**  
(54 days ago)

**Status**  
**Complete**

This task is waiting on  
Facilities

Last Update Submitted On  
Oct 20, 2016 Mar 30, 2016

Reference Number  
7228747

### Inspection Management Form

NDA-208780-ORIG-1

GENENTECH INC | 2917293 | REC NOT ELSEWHERE CLASSIFIED | [▼](#)

(b) (4)

ROCHE S.P.A. | 3003716872 | TCM TABLETS, PROMPT RELEASE | Approve Facility [▼](#)

(b) (4)

### Overall Manufacturing Inspection Recommendation

- Approve
- Withhold

[Cancel](#)

### Submission Manufacturing Facilities

Facility Status	Completion Date	Project Name	FEI	DUNS	Facility ID	Facility Name
No Further Evaluation	10/13/2016	<a href="#">NDA-208780-ORIG-1</a>	2917293	080129000	110005138	GENENTECH INC <a href="#">i</a> (b) (4)
Approve Facility	7/11/2016	<a href="#">NDA-208780-ORIG-1</a>				
Approve Facility	4/1/2016	<a href="#">NDA-208780-ORIG-1</a>	3003716872	430351356	110005037	ROCHE S.P.A. <a href="#">i</a> (b) (4)
Approve Facility	4/1/2016	<a href="#">NDA-208780-ORIG-1</a>				
Approve Facility	4/1/2016	<a href="#">NDA-208780-ORIG-1</a>				
Approve Facility	4/1/2016	<a href="#">NDA-208780-ORIG-1</a>				

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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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JONATHAN T DOW  
03/08/2017

**Recommendation: Approval**

**NDA 208780  
Review #1**

Drug Name/Dosage Form	Pirfenidone tablets
Strength	267, 534, 801 mg/tablet
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Genentech, Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
<i>Original</i>	<i>29-MAR-2016</i>	<i>All</i>
<i>Amendment</i>	<i>13-JUN-2016</i>	<i>Drug product</i>
<i>Amendment</i>	<i>30-JUN-2016</i>	<i>Drug product, drug substance</i>
<i>Amendment</i>	<i>07-JUL-2016</i>	<i>Facilities</i>
<i>Amendment</i>	<i>08-JUL-2016</i>	<i>Drug product</i>
<i>Amendment</i>	<i>29-JUL-2016</i>	<i>Drug product</i>
<i>Amendment</i>	<i>23-AUG-2016</i>	<i>Drug substance, Drug product</i>
<i>Amendment</i>	<i>03-OCT-2016</i>	<i>Process</i>
<i>Amendment*</i>	<i>26-OCT-2016</i>	<i>Process, drug product</i>

**Quality Review Team**

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Martin Haber	II/Division of New Drug API
Drug Product	Chris Hough	IV/DNDPII
Process	Ted Chang	IV/DPAPII
Microbiology	Ted Chang	IV/DPAPII
Facility	Cassandra Abellard	II/DIA
Biopharmaceutics	Angela Lu	II/DB
Regulatory Business Process Manager	Florence Aisida	I/Division I
Application Technical Lead	Craig M. Bertha	IV/DNDPII
Laboratory (OTR)		
ORA Lead		
Environmental Analysis (EA)		

## Quality Review Data Sheet

### 1. RELATED/SUPPORTING DOCUMENTS

#### A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	III		(b) (4)	Not reviewed		Sufficient information in application
	IV			Not reviewed		Sufficient information in application
	III			Not reviewed		Sufficient information in application
	II			Adequate	06-SEP-2016	

#### B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	67284	Genentech's IND for pifrenidone SODFs
NDA	22535	NDA for pifrenidone capsules from Genentech

### 2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

## Executive Summary

### I. Recommendations and Conclusion on Approvability

Based on the reviews and recommendations from the drug substance, drug product, biopharmaceutics, process, and facilities teams outlined in the review below, an overall recommendation of **approval** is to be forwarded to the clinical Division (DPARP).

A shelf-life or expiration dating period of 18 months is granted for all strengths of the drug product.

### II. Summary of Quality Assessments

#### A. Product Overview

The Agency approved a 267 mg capsule form of pirfenidone from Genentech under NDA 22535 for the treatment of idiopathic pulmonary fibrosis (IPF). The current application, also from Genentech, is for the approval of a more convenient set of strengths (267, 534, and 801 mg/tablet), as (immediate release) tablets, to reduce the number of dosage forms needed to be administered with dose escalation, for patients treated for IPF.

<b>Proposed Indication(s) including Intended Patient Population</b>	Idiopathic pulmonary fibrosis (IPF)
<b>Duration of Treatment</b>	Chronic
<b>Maximum Daily Dose</b>	Recommended daily maintenance dose is 2403 mg/day
<b>Alternative Methods of Administration</b>	No other routes of administration than oral

#### B. Quality Assessment Overview

There are two separate suppliers of the drug substance, pirfenidone. Pirfenidone is an achiral molecule that exists in solid state under ambient conditions. The drug is sparingly soluble in water and has no ionizable groups. (b) (4)

The process controls are adequate and characterization studies support the proposed chemical structure. Drug substance-related impurities are adequately characterized and controlled. The specification includes tests and acceptance criteria for identity, water content, residue on ignition, melting range, heavy metals, assay, related impurities, and particle size, and it is also supported by batch data. The drug substance has a high level of purity and is extremely stable with no degradation

observed on stability or during stress testing. The retest period for the drug substance is (b) (4) years when stored (b) (4).

The drug load of the tablets (all three strengths), is (b) (4) (w/w) and compendial-grade and common excipients are used. Tablets are distinguished by size and color (all have same shape and imprint, however). A single HDPE bottle container closure system is proposed for the drug product. The applicant has provided only 9 months of stability data and apparently makes no argument to leverage previously submitted stability data for their approved capsule version of this drug. The limited 9 months of stability data support an expiry period of 18 months for all three strengths.

From the biopharmaceutics perspective, the Applicant's overall approach for bridging between the currently approved 267 mg hard capsule and the proposed new film-coated tablet formulations/strengths involved a determination of bioequivalence to compare 1 × 801 mg film-coated tablet with 3 × 267 mg hard capsules of pirfenidone. The lower strength film-coated tablets 267 and 534 mg were compared with the film-coated tablet 801 mg bio-batch by means of comparative *in vitro* dissolution profiles. The difference in the to-be-marketed formulation and the formulation used in the pivotal bioequivalence Study GP29830 is the tablet width (length × widths: 20 × 9.7 mm with bioequivalence batch vs. 20 × 9.3 mm with commercial batch). This minor change in dimensions was bridged by multi-media dissolution profiles in the same way as for the bio-waiver of the lower strength film-coated tablets.

The applicant has developed the proposed (b) (4) manufacturing process based on the process of their approved capsule product (NDA 22535). (b) (4)

(b) (4)

(b) (4). The process is controlled adequately for (b) (4)

The process produces drug product meeting the regulatory specification. The selected manufacturing process has been studied and validated adequately and registration batches are the same scale as those proposed for commercial production.

The application and associated inspectional documents for the facilities responsible for manufacturing Pirfenidone Tablet have been evaluated and there are no significant outstanding risks for these facilities, i.e., all facilities were found to be acceptable with no inspections required.

An overall recommendation of **approval** is to be forwarded to the clinical Division (DPARP) from OPF.

**C. Special Product Quality Labeling Recommendations (NDA only)**

N/A

**D. Final Risk Assessment (see Attachment)**

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

**BIOPHARMACEUTICS****Product Background:****NDA: 208780****Drug Product Name / Strength: Pirfenidone 267, 534, and 801 mg/tablet****Route of Administration: Oral****Applicant Name: Genentech, Inc.*****Review Summary:***

The Applicant submitted a new NDA for Esbriet (pirfenidone) film-coated tablets for the treatment of patients with idiopathic pulmonary fibrosis (IPF). Esbriet film-coated tablets (267 mg, 534 mg, and 801 mg) are being developed to complement the approved 267 mg hard capsule formulation (NDA 22535). The three dosage forms of the film-coated tablets will support the approved dose escalation regimen for Esbriet in IPF and reduce the pill burden for patients (from nine capsules to three tablets for the daily maintenance dose). The Applicant cross-referenced NDA 22535 for Esbriet (pirfenidone) capsules (approved on 10/15/2014).

(b) (4)



**Table 1: Quantitative Composition of Pirfenidone Film-Coated Tablets, 267, 534, and 801 mg**

(b) (4)			F09	F10	F11; F12	% w/w
Strength			267 mg	534 mg	801 mg	
Component	Function	Specification	mg/unit	mg/unit	mg/unit	
Pirfenidone	Active	In-house	267.000	534.000	801.000	84.23
Microcrystalline cellulose	(b) (4)	NF/Ph. Eur.	(b) (4)			
(b) (4)		NF/ Ph. Eur.	(b) (4)			
Povidone	(b) (4)	USP/ Ph. Eur.	(b) (4)			
Croscarmellose sodium		NF/ Ph. Eur.	(b) (4)			
Magnesium stearate		NF/ Ph. Eur.	(b) (4)			
(b) (4)		NF/ Ph. Eur.	(b) (4)			
<b>Total (tablet core)</b>			(b) (4)			

NF= National Formulary; Ph. Eur.= European Pharmacopeia; w/w= weight/weight.

Dissolution Method:

The proposed in vitro dissolution method for Pirfenidone tablets is as follows:

Apparatus	Ph. Eur./USP II
Paddle Speed	50 ± 2 rpm
Medium	Water
Volume	1000 mL
Temperature	37°C ± 0.5°C
Samples	6 × 1 tablet
Sampling Times	5, 10, 15, 20, 30, 45 minutes
Quantification	UV at 312 nm
Filter	1 µm pore size (e.g. Pall 25 mm Acrodisc 1 µm glass fiber filter)

The proposed dissolution specification for pirfenidone film-coated tablets is NLT <sup>(b) (4)</sup>% (Q) in 30 minutes. All strengths of pirfenidone film-coated tablets release at least <sup>(b) (4)</sup>% in 30 minutes in water (selected medium) and three other media (HCl 0.1 N, Acetate pH 4.5, and Phosphate pH 6.8).

Waiver of Bioequivalence studies

➤ Biowaiver for lower strengths film-coated tablets 267 mg and 534 mg

The Applicant requested a biowaiver for the two lower dose strengths, 267 mg and 534 mg of Pirfenidone film-coated IR tablets. The biowaiver request is based on the following:

1. The Drug Product is in the same dosage form, but in a different strength.
2. The products are manufactured by the same manufacturing process.
3. The qualitative composition of the different strengths is the same.
4. The different strengths are proportionally similar in their active and inactive ingredients/quantitatively proportional <sup>(b) (4)</sup> to the strength used in the in vivo bioequivalence study.
5. Appropriate in vitro dissolution data confirm the adequacy of waiving the additional strengths.

The lower strengths, 267 mg and 534 mg are proportionally similar to 801 mg strength:

- Tablet cores: <sup>(b) (4)</sup>  
(see Table 4 below).
- Film-coat: <sup>(b) (4)</sup>

The biowaiver requirements are met for the lower strengths of 267 mg and 534 mg, and thus a biowavier is granted for the 267 mg and 534 mg strengths.

➤ Minor change of dimensions of 801 mg film-coated tablets

For the 801 mg strength tablet, oval shaped toolings of slightly different dimensions were used in formulation development (20.0 × 9.3 mm) and at registration scale (20.0 × 9.7 mm).

Comparative dissolution profiles were generated for the 801 mg commercial trade dress (b) (4)

(b) (4)

(b) (4) values and compared with the dissolution profiles of the 801 mg film-coated tablets bio-batch (b) (4) used in the bioequivalence Study. Dissolution profiles of the 801 mg film-coated tablets with the final commercial trade dress (dimensions 20.0 × 9.3 mm), at both low and high compression force, were shown to be similar to the dissolution profiles of the bio-batch as more than (b) (4) % of the drug is dissolved within 15 minutes in all media tested. Therefore, since there is no other change except for the minor dimensions (20.0 × 9.3 mm vs. 20.0 × 9.7 mm), the biowaiver is granted.

**List Submissions being reviewed (table):**

[Application 208780 - Sequence 0000 - 0000 \(1\) 03/29/2016 ORIG-1 /Multiple Categories/Subcategories](#)

**Highlight Key Outstanding Issues from Last Cycle: None**

**Concise Description Outstanding Issues Remaining: None**

***BCS Designation***

**Reviewer's Assessment: BCS class I molecule based on high aqueous solubility and high permeability.**

**Solubility:** Pirfenidone is very soluble in methanol, as well as freely soluble in ethyl alcohol and acetone. It is sparingly soluble in 1.0 N hydrochloric acid and 1.0 N sodium hydroxide. Its solubility in water is 18 - 21 mg/mL at 25°C over a pH range of 1 to 10.

**Permeability:** The in vitro permeability of pirfenidone was determined using Caco-2 cells. Apical to basal (A to B) transport of [14C]-pirfenidone was studied at 10, 100, 1000 μM. The apparent permeability of pirfenidone was 3.2E-05, 2.9E-05, and 2.7E-05 at concentration of 10, 100, and 1000 μM, respectively (Table 21). At all three concentrations, the A to B permeability of pirfenidone was greater than that of the high permeability comparator propranolol. Pirfenidone is therefore classified as a high permeability compound.

**Dissolution:**

Apparatus	Ph. Eur./USP II
Paddle Speed	50 ± 2 rpm
Medium	Water
Volume	1000 mL
Temperature	37°C ± 0.5°C
Samples	6 × 1 tablet
Sampling Times	5, 10, 15, 20, 30, 45 minutes
Quantification	UV at 312 nm
Filter	1 µm pore size (e.g. Pall 25 mm Acrodisc 1 µm glass fiber filter)

***Dissolution Method and Acceptance Criteria***

**Reviewer’s Assessment:**

**Drug Product**

**1. Dissolution Method**

**In vitro dissolution method for Pirfenidone tablets:**

Apparatus	Ph. Eur./USP II
Paddle Speed	50 ± 2 rpm
Medium	Water
Volume	1000 mL
Temperature	37°C ± 0.5°C
Samples	6 × 1 tablet
Sampling Times	5, 10, 15, 20, 30, 45 minutes
Quantification	UV at 312 nm
Filter	1 µm pore size (e.g. Pall 25 mm Acrodisc 1 µm glass fiber filter)

**Dissolution Method Development:**

(b) (4)

*Reviewer's comments for dissolution method development:*

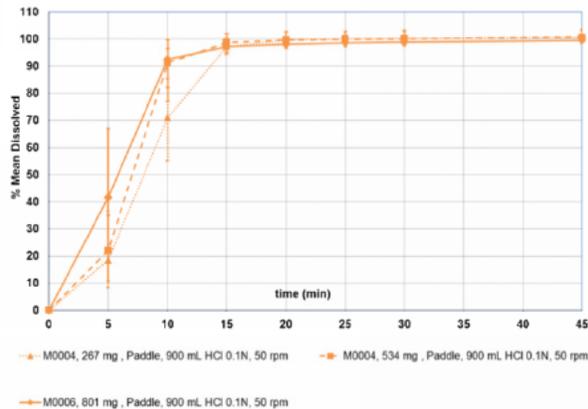
*The dissolution method is discriminatory towards different conditions, and the method is acceptable.*

### Dissolution Acceptance Criterion

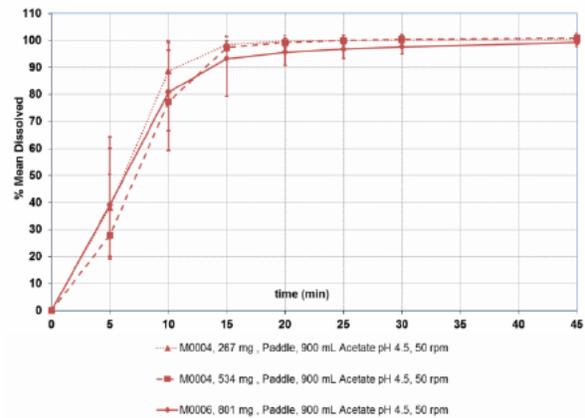
The proposed dissolution specification for pirfenidone film-coated tablets is NLT  $(b)_{(4)}\%$  (Q) in 30 minutes. Figure 13 below shows the comparative dissolution profiles for clinical batch of 801 mg strength and lower strengths of 267 mg and 534 mg in four different dissolution media. All strengths of pirfenidone film-coated tablets release at least  $(b)_{(4)}\%$  in 30 minutes in water (selected medium) and three other media.

**Figure 13: Comparative Dissolution Profiles of the Film-Coated Tablets 801 mg Bio-Batch and the Lower Strengths 267 and 534 mg Film-Coated Tablets (Biowaiver) in Four Different Media**

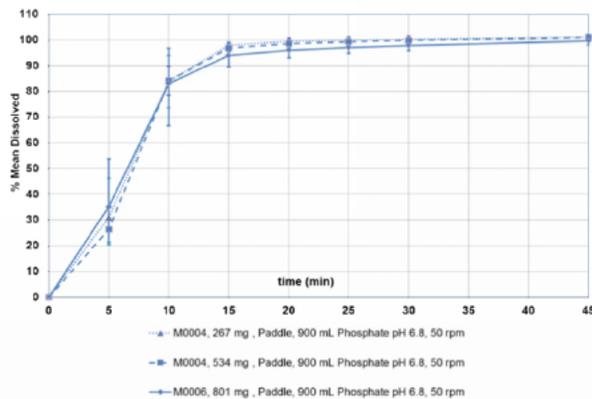
A) Medium: HCl 0.1N



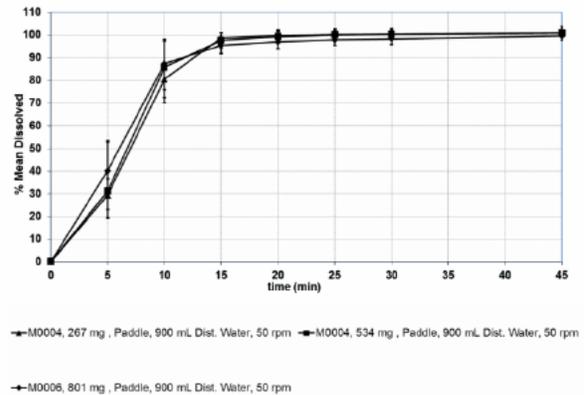
B) Medium: Acetate pH 4.5



C) Medium: Phosphate pH 6.8



D) Medium: Water



The Applicant conducted the long term stability testing with four batches of each strength with 6 dosage units. The stability data showed that all 12 batches tested meet the acceptance criterion (drug release at 30 min  $(b)_{(4)}\%$ ) at room temperature up to 6 months. Long term stability was tested at 30°C/75% relative humidity.

*Reviewer's comments:*

*Pirfenidone film-coated tablets appear to be immediate release in that they have at least  $\frac{(b)}{(4)}$ % of the drug released at 15 minutes. Based on the dissolution data, the proposed acceptance criterion of NLT  $\frac{(b)}{(4)}$ % (Q) in 30 minutes is reasonable.*

## **2. Analytical Method Validation-Linearity**

The linearity was validated over the range from 35% of low dosage strength to 120% of high dosage strength of test concentration with the correlation coefficient ( $r$ )  $\geq 0.99$ . The linearity is adequately validated.

*Clinical relevance of dissolution method & acceptance criteria (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)*

**Reviewer's Assessment: n/a**

*Application of dissolution/IVIVC in QbD*

**Reviewer's Assessment: n/a**

**MODIFIED RELEASE ORAL DRUG PRODUCTS –In-Vitro Alcohol Dose Dumping**

**Reviewer's Assessment: This is an immediate release drug product, and in vitro alcohol dose dumping study is not needed.**

*In-Vitro Soft-food Interaction Study*

**Reviewer's Assessment: n/a**

*In-Vitro Release Testing (IVRT) for Semi-Solid Products*

**Reviewer's Assessment: n/a**

*In-Vitro Permeation Testing (IVPT) for Transdermal/Topical Products*

**Reviewer's Assessment: n/a**

***In-Vitro Dissolution Testing for Abuse-deterrent Products*****Reviewer's Assessment: n/a*****In-Vitro BE Evaluation for Pulmonary Products*****Reviewer's Assessment: n/a*****EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim*****Reviewer's Assessment: n/a*****Bridging of Formulations*****Reviewer's Assessment: n/a*****Biowaiver Request*****Reviewer's Assessment:**Biowaiver for lower strengths film-coated tablets 267 mg and 534 mg

The Applicant requested a biowaiver for the two lower dose strengths, 267 mg and 534 mg of Pirfenidone film-coated IR tablets. The biowaiver request is based on the following:

6. The Drug Product is in the same dosage form, but in a different strength.
7. The products are manufactured by the same manufacturing process.
8. The qualitative composition of the different strengths is the same.
9. The different strengths are proportionally similar in their active and inactive ingredients/quantitatively proportional (b) (4) to the strength used in the in vivo bioequivalence study.
10. Appropriate in vitro dissolution data confirm the adequacy of waiving the additional strengths.

The lower strengths, 267 mg and 534 mg are proportionally similar to 801 mg strength:

- Tablet cores: (b) (4)  
(see Table 4 below).

- Film-coat:

(b) (4)

vary

(see Table 5 below)

**Table 4: Quantitative Composition of Pirfenidone Film-Coated Tablets, 267, 534, and 801 mg**

(b) (4)			F09	F10	F11; F12	
			267 mg	534 mg	801 mg	% w/w
Component	Function	Specification	mg/unit	mg/unit	mg/unit	
Pirfenidone	Active	In-house				(b) (4)
Microcrystalline cellulose	(b) (4)	NF/Ph. Eur.				
(b) (4)		NF/ Ph. Eur.				
Povidone (b) (4)		USP/ Ph. Eur.				
Croscarmellose sodium		NF/ Ph. Eur.				
Magnesium stearate		NF/ Ph. Eur.				
(b) (4)		NF/ Ph. Eur.				
<b>Total (tablet core)</b>						

NF = National Formulary; Ph. Eur. = European Pharmacopeia; w/w = weight/weight.

**Table 5: Quantitative Composition of Film Coating Mixtures Used in Pirfenidone Film Coated Tablets**

Dose Strength		267 mg	534 mg	801 mg
Product code		(b) (4)		
Quantitative Composition	Reference to Standard			
Polyvinyl alcohol, partially hydrolyzed	USP, Ph. Eur.			
Titanium dioxide	USP, Ph. Eur.			
Macrogol/ Polyethylene glycol (b) (4)	NF, Ph. Eur.			
Talc	USP, Ph. Eur.			
Iron oxide black	NF, E172			
Iron oxide red	NF, E172			
Iron oxide yellow	NF, E172			
<b>Total</b>				

NF = National Formulary; Ph. Eur. = European Pharmacopeia; w/w = weight/weight.

The comparative dissolution profiles of all three strengths in (b) (4) as well as in the proposed commercial dissolution medium (b) (4) are shown in Figure 13. All three strengths have at least (b) (4)% of the labeled claim dissolved in (b) (4) minutes, and thus are considered immediate release. The dissolution profiles of the three strengths are similar.

*Reviewer's comments:*

*The biowaiver requirements are met for the lower strengths of 267 mg and 534 mg, and thus a biowavier is granted for the 267 mg and 534 mg strengths.*

Minor change of dimensions of 801 mg film-coated tablets

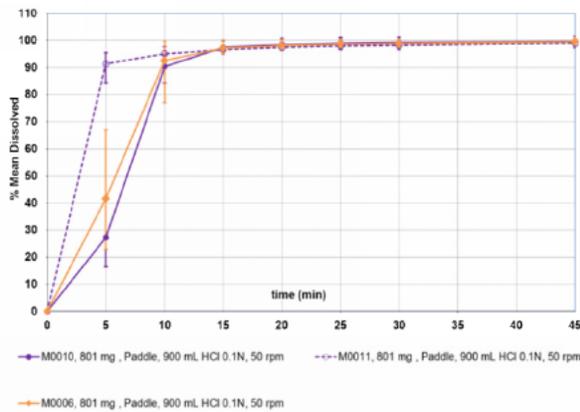
For the 801 mg strength tablet, oval shaped toolings of slightly different dimensions were used in formulation development ( $20.0 \times 9.3$  mm) and at registration scale ( $20.0 \times 9.7$  mm).

Comparative dissolution profiles were generated for the 801 mg commercial trade dress (b) (4) (b) (4)

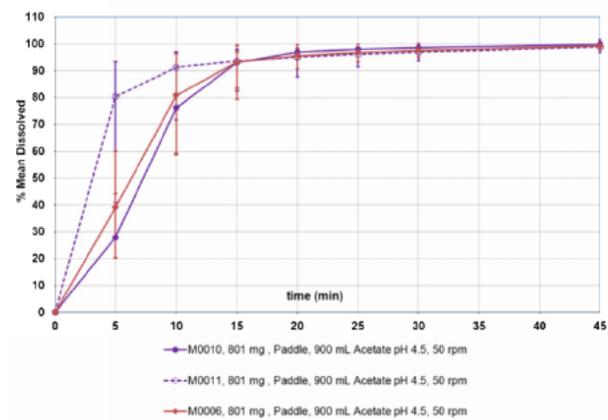
(b) (4) values and compared with the dissolution profiles of the 801 mg film-coated tablets bio-batch (b) (4) used in the bioequivalence Study. Dissolution profiles of the 801 mg film-coated tablets with the final commercial trade dress (dimensions  $20.0 \times 9.3$  mm), (b) (4) were shown to be similar to the dissolution profiles of the bio-batch as more than (b) (4)% of the drug is dissolved within 15 minutes in all media tested (Figure 14).

**Figure 14: Comparative Dissolution in Four Different Media of 801 mg Film-Coated Tablets Bio-Batch versus New Dimensions (Commercial Trade Dress) at Two Different Compression Forces/Solid Fractions**

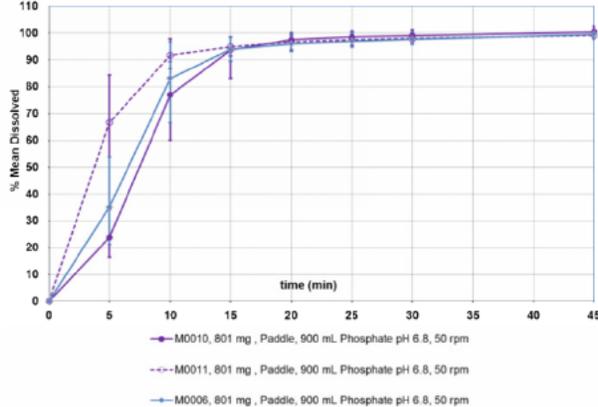
A) Medium: HCl 0.1N



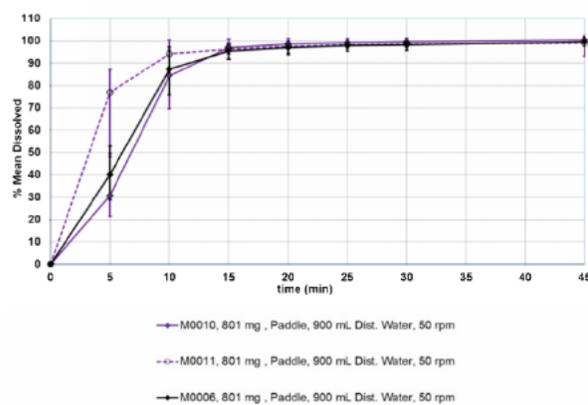
B) Medium: Acetate pH 4.5



C) Medium: Phosphate pH 6.8



D) Medium: Water



*Reviewer's comments:*

*The dissolution profiles of 801 mg commercial trade dress at low and high compression force and 801 mg film-coated tablets bio-batch are considered similar in that they dissolved at least (b) (4) % of the labeled claim in 15 minutes. Since there is no other change except for the minor dimensions (20.0 × 9.3 mm vs. 20.0 × 9.7 mm), the biowaiver is granted.*

**R Regional Information**

*Comparability Protocols*

**Reviewer's Assessment: n/a**

*Post-Approval Commitments*



**Reviewer's Assessment: n/a**

*Lifecycle Management Considerations*

**Reviewer's Assessment: n/a**

*List of Deficiencies: None.*

*Primary Biopharmaceutics Reviewer Name and Date: An-chi (Angela) Lu, Pharm D.  
10/17/2016*

*Secondary Reviewer Name and Date (and Secondary Summary, as needed):*

*I have reviewed the Biopharmaceutics section of the review and I concur with the above conclusions*

*Haritha Mandula, Ph.D., Acting Biopharmaceutics Lead, 10/25/2016.*

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# CHAPTER IV: Labeling

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ESBRIET safely and effectively. See full prescribing information for ESBRIET.

ESBRIET® (pirfenidone) capsules and film-coated tablets, for oral use

Initial U.S. Approval: 2014

## 3 DOSAGE FORMS AND STRENGTHS

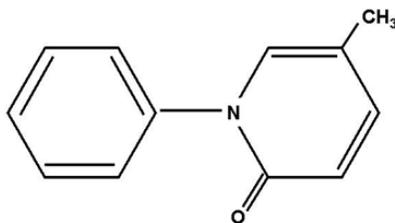
Capsules: 267 mg, white, hard gelatin capsules printed with “PFD 267 mg” on the cap of the capsule in brown ink.

Film-coated tablets: oval, biconvex, debossed with “PFD”, containing 267 mg (yellow), (b) (4) 801 mg (brown) pirfenidone

## 11 DESCRIPTION

ESBRIET belongs to the pyridone class of (b) (4). ESBRIET is available as a white hard gelatin capsule containing 267 mg of pirfenidone for oral administration, or, as film-coated tablets containing 267 mg (yellow), (b) (4) and 801 mg (brown) pirfenidone.

Pirfenidone has a molecular formula of  $C_{12}H_{11}NO$  and a molecular weight of 185.23. Pirfenidone has the following structural formula, which has been referred to as 5-methyl-1-phenyl-2-(1H)-pyridone or 5-methyl-1-phenyl-2-(1H)-pyridone.



Pirfenidone is a white to pale yellow, non-hygroscopic powder. It is more soluble in methanol, ethyl alcohol, acetone and chloroform than in water and 1.0 N HCl. The melting point is approximately 109°C.

ESBRIET capsule contains pirfenidone and the following inactive ingredients: microcrystalline cellulose, croscarmellose sodium, povidone, and magnesium stearate.

In addition, the capsule shell contains gelatin and titanium dioxide. The capsule brown printing ink includes shellac, iron oxide black, iron oxide red, iron oxide yellow, propylene glycol, ammonium hydroxide.

ESBRIET tablets contain pirfenidone and the following inactive ingredients:

Microcrystalline cellulose, colloidal anhydrous silica, povidone, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, macrogol (polyethylene glycol), talc, and iron oxide. (b) (4)

## 16 HOW SUPPLIED/STORAGE AND HANDLING

ESBRIET white hard gelatin capsules contain 267 mg of pirfenidone. The cap of the capsule is printed with “PFD 267 mg” in brown ink. The capsule is supplied either in a bottle, a 14-day titration blister pack or a 4-week maintenance blister pack.

ESBRIET film-coated tablets are oval, biconvex, debossed with “PFD”, containing 267 mg (yellow) and 801 mg (brown) pirfenidone. The film-coated tablets are supplied in bottles.

ESBRIET capsules:

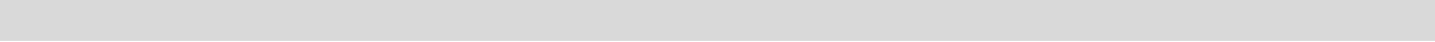
- NDC 50242-121-01, bottle for a 30-day supply containing 270 capsules and closed with a child-resistant closure
- NDC 50242-121-02, 14-day titration blister pack, carton containing a total of 63 capsules in two blister cards – a Week 1 blister card containing 21 capsules (1 capsule per blister well) and a Week 2 blister card containing 42 capsules (2 capsules per blister well)
- NDC 50242-121-03, 4-week maintenance blister pack, carton containing a total of 252 capsules in four blister cards each with 63 capsules (3 capsules per blister well)

ESBRIET film-coated tablets:

- NDC 50242-122-05, carton containing 3 bottles, each containing ninety 267 mg tablets (270 tablets total) with a child-resistant closure
- NDC 50242-123-01, carton containing 1 bottle containing ninety 801 mg tablets, with a child-resistant closure

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) (see USP Controlled Room Temperature).

Keep the bottle tightly closed. Do not use if the seal over the bottle opening is broken or missing.



***List of Deficiencies: None,***

***Primary Drug Product Reviewer Name and Date:***

***Secondary Drug Product Reviewer Name and Date:***

**{For NDA only}**

**R Regional Information**

**1.14 Labeling**

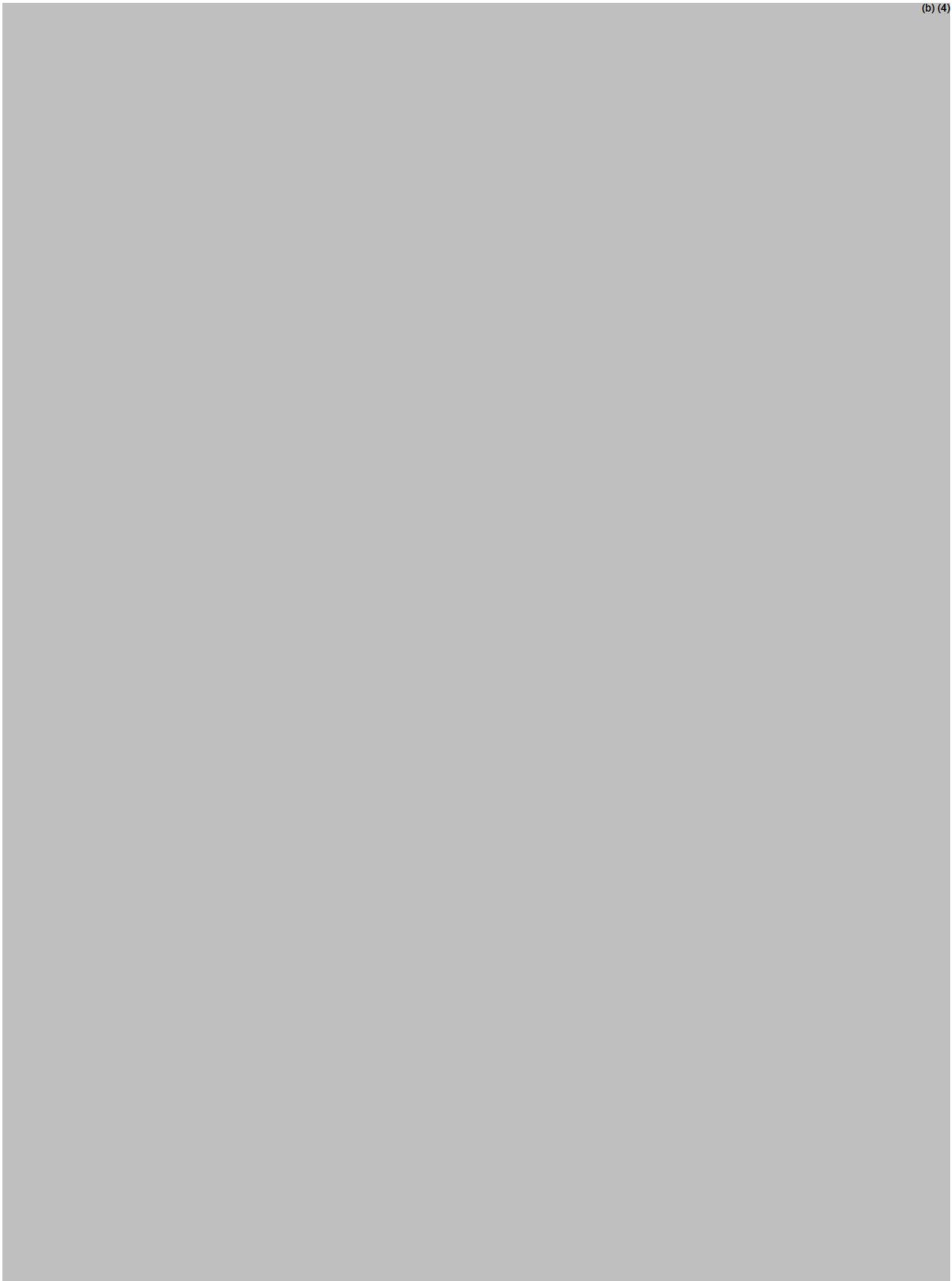
***Immediate Container Label***

(b) (4)



**Reviewer's Assessment:**

***The immediate container labels contain all required content and formatting. Only the 267 mg and 801 mg labels have been provided.***



**Reviewer's Assessment:**

**Carton labels comply with all requirements. Only the 267 mg and 801 mg labels have been provided.**

**List of Deficiencies: None**

**Primary Labeling Reviewer Name and Date:**

**Secondary Reviewer Name and Date (and Secondary Summary, as needed):**

## **ENVIRONMENTAL ANALYSIS**

### **R Regional Information**

The Applicant has followed the Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements, 1998. Their assessment does not meet the criteria described in Tier O approach. As a result, they have conducted the studies required to assess absorption, metabolism, life time and fate of drug released into the natural environment.

Absorption and Metabolism: Pirfenidone is rapidly absorbed in rats and dogs and metabolized with a half-life of 2 to 3.5 hours. Pirfenidone is converted to a 5-hydroxymethyl metabolite and then to the inactive 5-carboxylic acid metabolite. Most of pirfenidone is eliminated in the urine as hydrophilic metabolites (in particular the 5-carboxylic acid: 80 – 85% from rats and dogs, 97% from mice). Studies in humans showed similar results. The octanol: water partition coefficient is 0.9, suggesting that 90% of pirfenidone is found in the aqueous environment. Studies of the biodegradability of pirfenidone show that it is not readily biodegraded in the environment, and most of the downstream degradants (b) (4) does not appear to hinder microbial growth.

Aerobic transformation in aquatic sediment system was studied in two natural aquatic systems. <sup>14</sup>C-pirfenidone (labelled phenyl) was followed in these environments. The rate of dissipation of radiolabelled pirfenidone from the water and sediments was measured. <sup>14</sup>C levels in the aqueous phase fell from (b) (4)% of applied label at day 1 to (b) (4)% at day 14 and (b) (4)% at day 99. In the sediments radiolabelled carbon increased from (b) (4)% at the start to (b) (4)% on day 14, and (b) (4)% by day 99. The low level of total degradation was indicated by the production of <sup>14</sup>CO<sub>2</sub>, which by day 99 reached (b) (4)% of applied label. The two natural environments gave similar data.

To calculate the maximum expected emitted concentration an expected environmental concentration were based on there being no depletion mechanisms and were calculated based on the 5<sup>th</sup> year projected estimates- both the worst case scenarios. The expected introduction concentration from use is estimated at (b) (4) liters per day through publicly owned treatment works. No metabolism or depletion mechanisms are assumed.

No appreciable release of pirfenidone in the air is expected.

Toxicity studies were performed for the aquatic environment: Daphnia magna acute toxicity and early life stage toxicity in fish and algal growth inhibition were studied. The NOEC of pirfenidone for Daphnia magna is considered to be (b) (4), for early life stage fish it is (b) (4) and (b) (4) for respiration inhibition testing of sludge, which is the highest concentration below the EC20 at which the observed level of inhibition was below the accepted level of variability for the controls (b) (4)%. Several other studies were conducted. The results of these are similar to those mentioned above.

The calculation of the maximum expected environmental concentration (MEEC), the expected environmental concentration (EEC), and the Expected Introduction Concentration (EIC) from patient use are:

(b) (4)

This estimate demonstrates that the criteria for Tier 2 are met

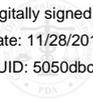
**Reviewer's Assessment:**

***The environment assessment given by the applicant has be thorough and is adequate.***



Julia  
Pinto

Digitally signed by Julia Pinto  
Date: 11/28/2016 10:53 33AM  
GUID: 5050dbcb00001294a888a4bdc20a3a58



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# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

Application #: 208780      Submission Type: 505(b)(1)

Established/Proper Name:  
pirfenidone

Applicant: Genentech, Inc.      Letter Date: 29-MAR-2016

Dosage Form: tablets

Chemical Type: non-NME      Stamp Date: 29-MAR-2016

Strength: 267, 534, and 801 mg/tablet

A. FILING CONCLUSION				
	Parameter	Yes	No	Comment
1.	<b>DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?</b>	X		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			N/A
3.	Are there any <b>potential review</b> issues to be forwarded to the Applicant, not including any filing comments stated above?	X		<b>IR Comment for NDA Applicant:</b> Contact the holders of the referenced DMFs and have them resubmit letters of authorization that provide sufficient information to allow us to locate the information referenced for your application (i.e., amendment date(s), page numbers).

B. NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
<b>Product Type</b>				
1.	New Molecular Entity <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
2.	Botanical <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
3.	Naturally-derived Product	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
4.	Narrow Therapeutic Index Drug	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
5.	PET Drug	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
6.	PEPFAR Drug	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
7.	Sterile Drug Product	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
8.	Transdermal <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
9.	Pediatric form/dose <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
10.	Locally acting drug <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
11.	Lyophilized product <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
12.	First generic <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
13.	Solid dispersion product <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
14.	Oral disintegrating tablet <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
15.	Modified release product <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
16.	Liposome product <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
17.	Biosimilar product <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
18.	Combination Product	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
19.	Other	<input type="checkbox"/>	<input type="checkbox"/>	

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
<b>Regulatory Considerations</b>				
20.	USAN Name Assigned	<input checked="" type="checkbox"/>	<input type="checkbox"/>	pirfenidone
21.	Meeting Agreements (under IND 67284)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<p>27-MAY-2015, Written-Response Only (WRO):</p> <ul style="list-style-type: none"> <li>• Agreed applicant could submit 6 months of stability data in NDA with an additional 3 months provided within two months after NDA submission (by 29-MAY-2016)</li> <li>• Master batch record in Italian is to be translated into English for the 801 mg strength; executed batch records will be accepted in their original language</li> <li>• Applicant was asked to submit a detailed report outlining the selection of the dissolution test and acceptance criterion</li> </ul> <p>26-OCT-2015, Meeting:</p> <ul style="list-style-type: none"> <li>• A biowaiver for a lower strength (133 mg) film-coated tablet was discussed, but this strength is not included in this NDA (likely will be submitted under an sNDA)</li> </ul>
22.	SPOTS (Special Products On-line Tracking System)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application	<input type="checkbox"/>	<input type="checkbox"/>	Unknown
24.	Comparability Protocol(s) <sup>2</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
25.	Other _____	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Quality Considerations</b>				
26.	Drug Substance Overage	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
27.	Design Space	Formulation	<input type="checkbox"/>	<input checked="" type="checkbox"/>
28.		Process	<input type="checkbox"/>	<input checked="" type="checkbox"/>
29.		Analytical Methods	<input type="checkbox"/>	<input checked="" type="checkbox"/>
30.		Other	<input type="checkbox"/>	<input checked="" type="checkbox"/>
31.	Real Time Release Testing (RTRT)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
32.	Parametric Release in lieu of Sterility Testing	<input type="checkbox"/>	<input type="checkbox"/>	N/A
33.	Alternative Microbiological Test Methods	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Reference to USP <61> and <62>
34.	Process Analytical Technology <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	<input checked="" type="checkbox"/>	<input type="checkbox"/>
36.		Excipients	<input checked="" type="checkbox"/>	<input type="checkbox"/>
37.		Microbial	<input type="checkbox"/>	<input checked="" type="checkbox"/>
38.	Unique analytical methodology <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
39.	Excipients of Human or Animal Origin	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
40.	Novel Excipients	<input type="checkbox"/>	<input checked="" type="checkbox"/>	For Opadry II film coating mixtures

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

B. NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
41.	Nanomaterials <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
42.	Hold Times Exceeding 30 Days	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
43.	Genotoxic Impurities or Structural Alerts	<input checked="" type="checkbox"/>	<input type="checkbox"/>	See S.3.2 (b) (4)
44.	Continuous Manufacturing	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
45.	Other unique manufacturing process <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
47.	New delivery system or dosage form <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
48.	Novel BE study designs	<input type="checkbox"/>	<input type="checkbox"/>	Unknown, refer to clinical pharmacology filing review
49.	New product design <sup>1</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Tablet dimensions for the 801 mg strength have changed during development to "improve appearance and processability"
50.	Other	<input type="checkbox"/>	<input type="checkbox"/>	N/A

<sup>1</sup>Contact Office of Testing and Research for review team considerations

<sup>2</sup>Contact Post Marketing Assessment staff for review team considerations

C. FILING CONSIDERATIONS					
	Parameter	Yes	No	N/A	Comment
<b>GENERAL/ADMINISTRATIVE</b>					
1.	Has an environmental assessment report or categorical exclusion been provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Will require consult to EA team for review
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? <input type="checkbox"/> Drug Substance <input type="checkbox"/> Drug Product <input type="checkbox"/> Appendices <ul style="list-style-type: none"> <li><input type="checkbox"/> Facilities and Equipment</li> <li><input type="checkbox"/> Adventitious Agents Safety Evaluation</li> <li><input type="checkbox"/> Novel Excipients</li> </ul> <input type="checkbox"/> Regional Information <ul style="list-style-type: none"> <li><input type="checkbox"/> Executed Batch Records</li> <li><input type="checkbox"/> Method Validation Package</li> <li><input type="checkbox"/> Comparability Protocols</li> </ul>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<ul style="list-style-type: none"> <li>• For the sections examined for the filing review (not all pages of the application were examined)</li> <li>• Note no appendices included in QOS</li> <li>• QOS is only a summary of module 3, thus a review is not necessary (as module 3 will be reviewed)</li> </ul>
<b>FACILITY INFORMATION</b>					
3.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Five (5) sites listed on Form 356h (3 for drug substance and 2 for drug product)

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

C. FILING CONSIDERATIONS				
	application list: <input type="checkbox"/> Name of facility, <input type="checkbox"/> Full address of facility including street, city, state, country <input type="checkbox"/> FEI number for facility (if previously registered with FDA) <input type="checkbox"/> Full name and title, telephone, fax number and email for on-site contact person. <input type="checkbox"/> Is the manufacturing responsibility and function identified for each facility, and <input type="checkbox"/> DMF number (if applicable)			
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: <input type="checkbox"/> Is a manufacturing schedule provided? <input type="checkbox"/> Is the schedule feasible to conduct an inspection within the review cycle?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
DRUG SUBSTANCE INFORMATION				
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review?  <input type="checkbox"/> general information <input type="checkbox"/> manufacture <ul style="list-style-type: none"> <li>○ Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)</li> <li>○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only</li> <li>○ Includes complete description of product lots and their uses during development – BLA only</li> </ul> <input type="checkbox"/> characterization of drug substance <input type="checkbox"/> control of drug substance <ul style="list-style-type: none"> <li>○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred)</li> <li>○ Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only</li> </ul> <input type="checkbox"/> reference standards or materials <input type="checkbox"/> container closure system	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
				<ul style="list-style-type: none"> <li>• Follows CTD formatting (note that not all pages of the application were examined)</li> <li>• Application does <i>not</i> include production data on the manufacture of the drug substance (no executed batch records for drug substance are included in the regional information section, however, this is not required by regulation under 21 CFR 314.50)</li> <li>• Application does include batch data for drug substance manufactured at the intended commercial site and with the intended commercial process</li> </ul>

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

C. FILING CONSIDERATIONS				
	<input type="checkbox"/> stability <ul style="list-style-type: none"> <li>○ Includes data establishing stability of the drug substance through the proposed retest period and a stability protocol describing the test methods used and time intervals for assessment</li> </ul>			
DRUG PRODUCT INFORMATION				
7.	Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? <ul style="list-style-type: none"> <li><input type="checkbox"/> Description and Composition of the Drug Product</li> <li><input type="checkbox"/> Pharmaceutical Development                             <ul style="list-style-type: none"> <li>○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots</li> <li>○ Includes complete description of product lots and their uses during development</li> </ul> </li> <li><input type="checkbox"/> Manufacture                             <ul style="list-style-type: none"> <li>○ If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter?</li> </ul> </li> <li><input type="checkbox"/> Control of Excipients</li> <li><input type="checkbox"/> Control of Drug Product                             <ul style="list-style-type: none"> <li>○ Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)</li> <li>○ Includes data to demonstrate process consistency (i.e. data on process validation lots)</li> <li>○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred)</li> <li>○ Analytical validation package for release test procedures, including dissolution</li> </ul> </li> <li><input type="checkbox"/> Reference Standards or Materials</li> <li><input type="checkbox"/> Container Closure System                             <ul style="list-style-type: none"> <li>○ Include data outlined in container closure guidance document</li> </ul> </li> <li><input type="checkbox"/> Stability                             <ul style="list-style-type: none"> <li>○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment</li> </ul> </li> </ul>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
				<ul style="list-style-type: none"> <li>• Two “major” changes to the manufacturing process following the production of the registration drug product batches are described</li> <li>• Drug product batch M0006 (801 mg) was used in the BE study and was also a registration stability batch listed in P.8.3</li> <li>• DMF letters of authorization are inadequate in that they do not provide sufficient detailed information about where to locate the referenced information (i.e., amendment date and page number)</li> <li>• Note the executed batch record is included for the BE study batch (M0006) of drug product manufactured at the intended commercial site (Roche, Segrate)</li> <li>• The applicant does not provide process validation data, but they have made multiple batches of each strength at the commercial site (the data for these can be used to assess process consistency to some extent)</li> <li>• One CCS is proposed for use (a 200 mL HDPE bottle with a tamper evident and child-resistant cap)</li> <li>• Six (6) months of long term (30°C/75%RH) and accelerated (40°C/75%RH) stability data are provided with testing intervals consistent with Q1A</li> <li>• No appendices are included, but there is a Regional Information section that includes master and executed batch records and a method validation summary with</li> </ul>

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

C. FILING CONSIDERATIONS					
	<input type="checkbox"/> APPENDICES <input type="checkbox"/> REGIONAL INFORMATION				reference to pertinent NDA sections
BIOPHARMACEUTICS					
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? <i>(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	In vitro dissolution data to bridge the minor change dimensions of 801 mg film-coated tablets between the batch used in bioequivalence study and to-be-marketed formulation
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	There is no request for BCS 1 designation. However, the applicant stated in their report that the drug substance is highly soluble (according to the Biopharmaceutical Classification System) across the physiological pH range and the drug product demonstrates <sup>(b) (4)</sup> dissolution in water (greater than <sup>(b) (4)</sup> % in 15 minutes).
REGIONAL INFORMATION AND APPENDICES					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	No executed batch records for drug substance are provided (but this is N/A)
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? <input type="checkbox"/> facilities and equipment <ul style="list-style-type: none"> <li><input type="checkbox"/> manufacturing flow; adjacent areas</li> <li><input type="checkbox"/> other products in facility</li> <li><input type="checkbox"/> equipment dedication, preparation, sterilization and storage</li> </ul>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

C. FILING CONSIDERATIONS					
	<ul style="list-style-type: none"> <li>○ procedures and design features to prevent contamination and cross-contamination</li> <li><input type="checkbox"/> adventitious agents safety evaluation (viral and non-viral) e.g.:                             <ul style="list-style-type: none"> <li>○ avoidance and control procedures</li> <li>○ cell line qualification</li> <li>○ other materials of biological origin</li> <li>○ viral testing of unprocessed bulk</li> <li>○ viral clearance studies</li> <li>○ testing at appropriate stages of production</li> </ul> </li> <li><input type="checkbox"/> novel excipients</li> </ul>				
17.	<p>Are the following information available for Biotech Products:</p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example:                             <ul style="list-style-type: none"> <li>○ LAL instead of rabbit pyrogen</li> <li>○ Mycoplasma</li> </ul> </li> </ul> <p>Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples</p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

### Biopharmaceutics Section

From the Biopharmaceutics perspective, this NDA is acceptable for filing.

### Summary:

The Applicant submits a new NDA for Esbriet (pirfenidone) film-coated tablets for the treatment of patients with idiopathic pulmonary fibrosis (IPF). Esbriet film-coated tablets (267 mg, 534 mg, and 801 mg) are being developed to complement the approved 267 mg hard capsule formulation (NDA 22535). The three dosage forms of the film-coated tablets will support the approved dose escalation regimen for Esbriet in IPF and reduce the pill burden for patients (from nine capsules to three tablets for the daily maintenance dose). The Applicant plans to cross-refer to NDA 22535 for Esbriet (pirfenidone) capsules (approved on 10/15/2014).

(b) (4)

# OFFICE OF PHARMACEUTICAL QUALITY

(b) (4)



**Table 1: Quantitative Composition of Pirfenidone Film-Coated Tablets, 267, 534, and 801 mg**

(b) (4)			F09	F10	F11; F12	% w/w
			267 mg	534 mg	801 mg	
Component	Function	Specification	mg/unit	mg/unit	mg/unit	
Pirfenidone	Active	In-house	(b) (4)			
Microcrystalline cellulose	(b) (4)	NF/Ph. Eur.				
(b) (4)		NF/ Ph. Eur.				
Povidone		USP/ Ph. Eur.				
Croscarmellose sodium		NF/ Ph. Eur.				
Magnesium stearate		NF/ Ph. Eur.				
(b) (4)		NF/ Ph. Eur.				
<b>Total (tablet core)</b>						

NF=National Formulary; Ph. Eur.=European Pharmacopeia; w/w=weight/weight.

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

### In Vitro Dissolution Testing:

The proposed dissolution method is as follows:

Apparatus	Ph. Eur./USP II
Paddle Speed	50 ± 2 rpm
Medium	Water
Volume	1000 mL
Temperature	37°C ± 0.5°C
Samples	6 × 1 tablet
Sampling Times	5, 10, 15, 20, 30, 45 minutes
Quantification	UV at 312 nm
Filter	1 µm pore size (e.g. Pall 25 mm Acrodisc 1 µm glass fiber filter)

Pirfenidone is a highly water-soluble molecule, with a pH-independent solubility of approximately 20 mg/mL across a pH range of 1–10. On the basis of high aqueous solubility and high permeability, pirfenidone exhibits the properties of a BCS Class I molecule.

The applicant submitted dissolution method development report, dissolution method validation report and raw data.

### Biowaiver Requests

*Biowaiver for lower strengths film-coated tablets 267 and 534 mg*

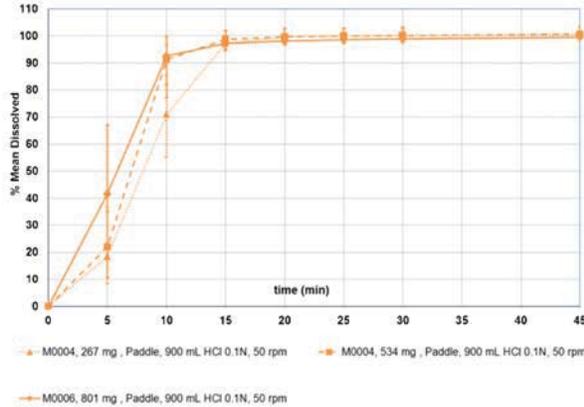
All film-coated tablet strengths are manufactured by the same manufacturing process and manufacturer. [REDACTED] (b) (4). The lower strengths film-coated tablets, 267 and 534 mg, are bridged to the film-coated tablets 801 mg (used in the bioequivalence study) by means of comparative dissolution. Figure 2 shows the comparative dissolution profiles of the three strengths in four different media. Similarity factor f2 are not calculated since more than (b) (4) % is dissolved within 15 minutes.

# OFFICE OF PHARMACEUTICAL QUALITY

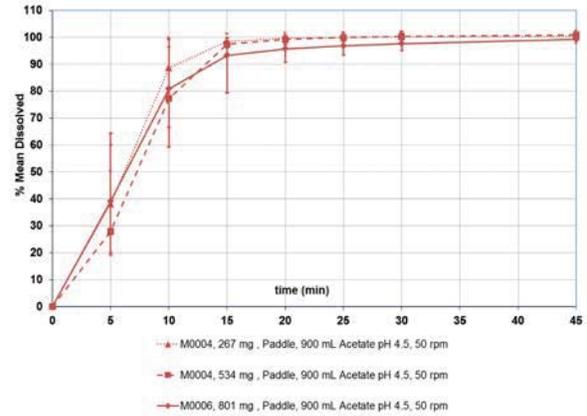
## FILING REVIEW

Figure 2: Comparative Dissolution Profiles of the Film-Coated Tablets 801 mg Bio-Batch and the Lower Strengths 267 and 534 mg Film-Coated Tablets (Biowaiver) in Four Different Media

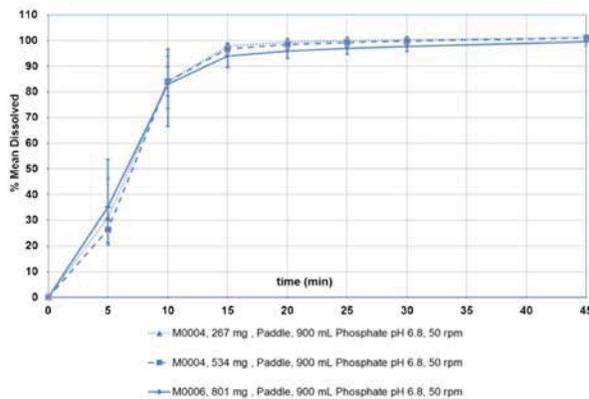
A) Medium: HCl 0.1N



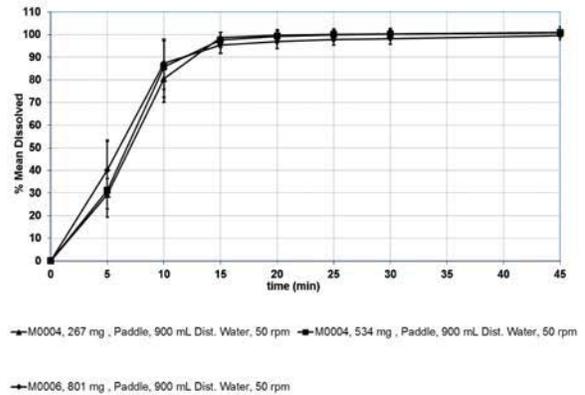
B) Medium: Acetate pH 4.5



C) Medium: Phosphate pH 6.8



D) Medium: Water



### Minor change of dimensions of 801 mg film-coated tablets

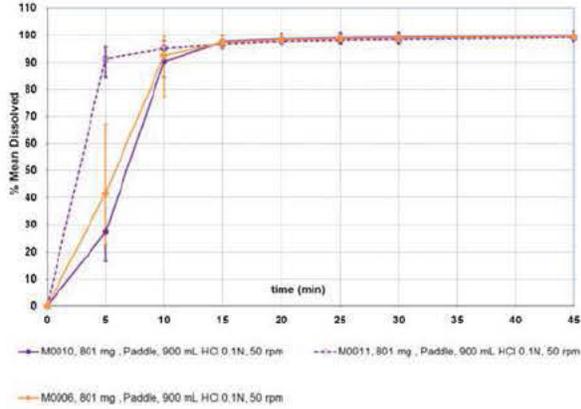
Comparative dissolution profiles were generated for the 801 mg commercial trade dress at (b) (4) [batch M0011] and (b) (4) [batch M0010] (b) (4) values and (b) (4) used in the bioequivalence Study. Dissolution profiles of the 801 mg film-coated tablets with the final commercial trade dress (dimensions 20.0 × 9.3 mm), (b) (4) were demonstrated to be similar to the dissolution profiles of the bio-batch as more than (b) (4) % of the drug is dissolved within 15 minutes in all media tested.

# OFFICE OF PHARMACEUTICAL QUALITY

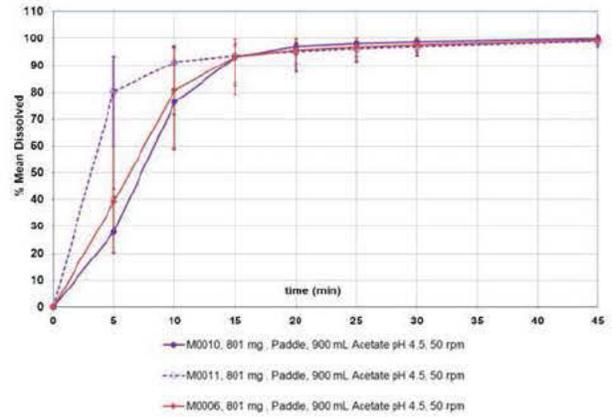
## FILING REVIEW

**Figure 3: Comparative Dissolution in Four Different Media of 801 mg Film-Coated Tablets Bio-Batch versus New Dimensions (Commercial Trade Dress) at Two Different Compression Forces/Solid Fractions**

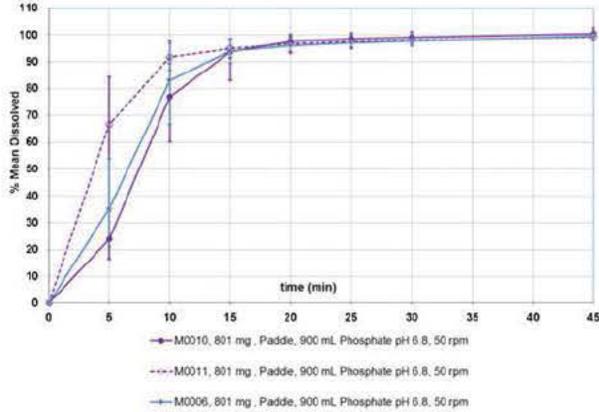
A) Medium: HCl 0.1N



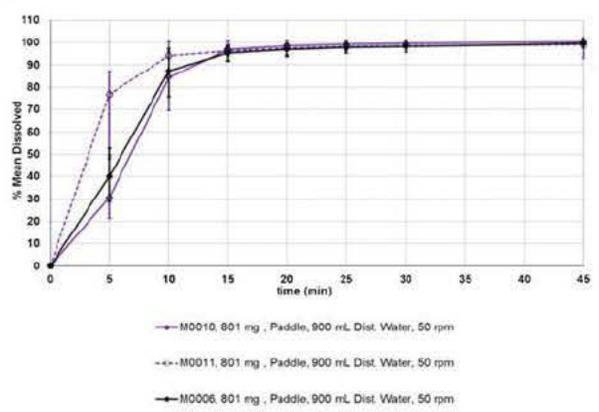
B) Medium: Acetate pH 4.5



C) Medium: Phosphate pH 6.8



D) Medium: Water



ONDQA Initial Quality Assessment (IQA) and Filing Review

For Pre-Marking Applications

NDA #: 208780

Received Date: 29-MAR-2016

Drug Product Risk Assessment

DP attribute/ CQA	Factors that can impact the CQA	O <sup>1</sup>	S <sup>1,2</sup>	D <sup>1</sup>	FMECA RPN #	Comment & considerations
Appearance	<ul style="list-style-type: none"> <li>(b) (4)</li> <li>appearance issue</li> <li>Variability of coating weight</li> </ul>	3	3	3	27	(b) (4)
Identification	<ul style="list-style-type: none"> <li>Incorrect drugs formulated</li> <li>No drug formulated</li> <li>Incorrect crystalline form of API</li> </ul>	2	3	3	18	<ul style="list-style-type: none"> <li>Drug product specification includes an examination of the appearance</li> <li>Probability of occurrence should be low and detectability high if applicant adheres to GMPs; specification for drug substance includes a specific (IR) identification test, consistent with Q6A</li> <li>Severity of failure would depend on situation (incorrect or no drug present)<sup>2</sup></li> <li>Applicant claims there is only (b) (4)</li> </ul>

<sup>1</sup> O = Probability of Occurrence; S = Severity of Effect; D = Detectability

<sup>2</sup> Severity of effect can only be estimated; input from clinical, clinical pharmacology, and pharmacology/toxicology team would be necessary for more accurate assessment of clinical impact of failures of product CQAs.

ONDQA Initial Quality Assessment (IQA) and Filing Review

For Pre-Marketing Applications

NDA #: 208780

Received Date: 29-MAR-2016

Drug Product Risk Assessment

<p>Content (assay)/Purity</p>	<p>3</p>	<p>3</p>	<p>2</p>	<p>18</p>	<p>(b) (4) (b) (4) of pirfenidone (they claim extensive screening was done but have not provided any details); there is no testing to confirm this form in the drug substance specification</p> <ul style="list-style-type: none"> <li>• Drug product specification has specific (IR spectral comparison) and non-specific (retention time comparison) to a reference</li> <li>• Total impurities allowed in input API limited by respective specification; heavy metals limited to NMT (b) (4) ppm; residue on ignition NMT (b) (4) %</li> <li>• Probability of occurrence of API dispensing errors should be low and detectability high if applicant adheres to GMPs</li> <li>• Applicant performed compatibility studies of the API and excipients (see P.2.1.1.2) with storage at (b) (4) with evaluation of appearance, crystalline form change, content (%w/w), and impurities; chosen excipients were said to be compatible but it is noted that povidone, Mg stearate, and croscarmellose Na yielded low pirfenidone content (b) (4) excipients are of compendial quality, i.e., suitable for solid oral dosage forms (proprietary film coating prepared from compendial ingredients as well)</li> <li>• IPCs include an examination of both individual and average tablet weight</li> <li>• Applicant claims in S.3.2.1.3 that there was no pirfenidone degradation observed during stability or during forced degradation studies, but the latter results were not detailed any further</li> <li>• There are no specific limits on residual solvents for the API, (b) (4); no organic solvents used in drug product manufacturing process</li> </ul>
<ul style="list-style-type: none"> <li>• Input purity of APIs</li> <li>• Incorrect amounts of API formulated</li> <li>• Impurity formation due to interaction of drugs with excipients or catalyzed by excipients</li> <li>• Low table weights</li> <li>• Degradation of drug substance (b) (4) (protection from environment)</li> <li>• Presence of organic solvents</li> <li>• CU problems (<i>vide infra</i>)</li> </ul>					

ONDQA Initial Quality Assessment (IQA) and Filing Review

For Pre-Marking Applications

NDA #: 208780

Received Date: 29-MAR-2016

Drug Product Risk Assessment

<p>Release (dissolution)</p>	<ul style="list-style-type: none"> <li>Polymorphic or pseudo-polymorphic (b) (4) conversion of drug substance</li> <li>Input API (b) (4) content</li> <li>Granule (b) (4) content</li> <li>Input API particle size change (two API sources)</li> <li>dried granule particle size</li> <li>Tablet (b) (4)</li> <li>Tablet (b) (4) is said to be a "critical material attribute" (b) (4)</li> </ul>	<p>3</p>	<p>3</p>	<p>3</p>	<p>27</p>	<ul style="list-style-type: none"> <li>Applicant claims that there is only (b) (4)</li> <li>Input particle size and moisture content of API are controlled by the specification (b) (4)</li> <li>(b) (4) acceptance criterion for the granules of product with acceptable release characteristics (b) (4)</li> <li>Pirfenidone is said not to be hygroscopic (b) (4)</li> </ul>
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ONDQA Initial Quality Assessment (IQA) and Filing Review

For Pre-Marketing Applications

NDA #: 208780 Received Date: 29-MAR-2016

Drug Product Risk Assessment

								(b) (4)
Content uniformity	<ul style="list-style-type: none"> <li>Lack of blend uniformity (BU) (b) (4)</li> <li>Particle size of API</li> </ul>	1	3	5	15	<ul style="list-style-type: none"> <li>The drug load is (b) (4) at about (b) (4)%, which will make achievement of BU easier</li> <li>Blending parameters are fixed at (b) (4)</li> <li>Individual tablet core weights are checked during (b) (4)</li> <li>There is no mention that the applicant will be performing blend uniformity testing during manufacturing (potential GMP issue that will be addressed by OPF)</li> <li>API specification has an upper limit on the particle size</li> <li>Content uniformity is tested as part of drug product specification as per USP &lt;905&gt;</li> </ul>		
Microbial limits <sup>3</sup>	<ul style="list-style-type: none"> <li>Microbial load of input materials for formulation</li> <li>Microbial contamination during processing (e.g., during tablet coating)</li> <li>Microbial growth during shelf life</li> </ul>	1	3	3	9	<ul style="list-style-type: none"> <li>Input materials must meet criteria for microbial limits</li> <li>cGMP requirements are said to be followed during manufacturing</li> <li>Microbial growth is unlikely (b) (4) in (b) (4) final dosage form</li> <li>Final drug product specification includes testing for microbial limits said to be consistent with the USP for non-aqueous oral drug products (presumably USP &lt;111&gt;)</li> </ul>		

Angela Lu, Biopharmaceutics Reviewer (5/05/2016)

Haritha Mandula, Biopharmaceutics Secondary Reviewer (5/05/2016)

Craig Bertha, ATL (5/06/2016)

<sup>3</sup> Evaluation to be done by the microbiology team/reviewer.

Craig M. Bertha - S  
 Digitally signed by Craig M. Bertha - S  
 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300103470, cn=Craig M. Bertha - S  
 Date: 2016.05.06 06:41:05 -04'00'

## Office of Pharmaceutical Quality

### NDA Reviewer Assignment Information

NDA # 208780	Established/Proper Name: pirfenidone
Dosage Form: Tablets (immediate release)	Strengths: 267, 534, and 801 mg/tablet
Applicant: Genentech, Inc.	Lead Branch: IV
BCS Class: I	Approximate Goal Date for Primary Review: 29-NOV-2016
Submission Type: 505(b)(1)	Goal Date for Action: 29-MAR-2017
Chemical Type: 3 - new dosage form	Cross Referenced Applications: NDA 22535 and IND 67284

#### A. PRODUCT/ PROCESS DESCRIPTION (Critical Information for Making Assignments)

Pirfenidone is approved for treatment of idiopathic pulmonary fibrosis under NDA 22535 with a capsule dosage form (Esbriet®). This application proposes three strengths of an immediate release film-coated tablet dosage form (267, 534, and 801 mg pirfenidone/tablet). The drug load is high at (b) (4)%. The drug substance is (b) (4). The formulation uses (b) (4). Manufacturing involves (b) (4). Excipients include the drug, microcrystalline cellulose, silica, povidone, croscarmellose Na, Mg stearate, and proprietary coating systems prepared with compendial grade components.

*Office of Pharmaceutical Quality*

**NDA Reviewer Assignment Information**

<b>B. APPLICATION ELEMENTS</b>				
<i>Initial Assessment</i>		<b>Y</b> <i>es</i>	<b>N</b> <i>o</i>	<b>Comments</b>
1.	Accelerated Review expected? (Priority or Breakthrough)		X	
2.	Narrow Therapeutic Index Drug		X	
3.	PET Drug, Drug Device Combination, Liposome product, Biosimilar product, Novel Dosage Form, Emerging Technology		X	
4.	Specialty Population (i.e., young children and/or elderly)		X	
5.	Sterile Drug Product (Aseptic, Terminal, Parametric Release)		X	
6.	Use of Models for Release (IVIVC, dissolution models for real time release)		X	
7.	DMF(s) referenced for drug substance?	X		DMF (b) (4)
	Never reviewed		X	
	Previously reviewed - acceptable	X		
	Previously reviewed – new amendments	X		2 Amendments and 2 ARs not reviewed

*Office of Pharmaceutical Quality*

**NDA Reviewer Assignment Information**

<b>B. APPLICATION ELEMENTS</b>				
<i>Initial Assessment</i>		<b>Y</b> <i>es</i>	<b>N</b> <i>o</i>	<b>Comments</b>
8.	Complex API (Polymeric molecules, Heterogeneous mixtures, Botanical, Antibody-Drug-Conjugate)		X	
9.	Real Time Release Testing, Continuous Manufacturing, PAT		X	
10.	EA Team: <ul style="list-style-type: none"> <li>• NMEs</li> <li>• API with estrogenic, androgenic, or thyroid activity</li> <li>• API derived from plants or animals</li> <li>• Environmental Assessments</li> </ul>	X		A 631 page EA document is included for review

Summarized by *[Electronic Signatures]*

<b>Signature and Date</b>	
<p>Title: CMC Lead (Division of Pulmonary, Allergy, and Rheumatology Products), ONDP, DNDPII, Branch IV</p> <p>Print Name: Craig M. Bertha</p>	
<p>Signature and Date:</p>	<p style="font-size: 1.2em; margin: 0;"><b>Craig M. Bertha -S</b></p> <p style="font-size: 0.8em; margin: 0;">Digitally signed by Craig M. Bertha -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300103470, cn=Craig M. Bertha -S Date: 2016.03.31 06:32:14 -04'00'</p>

# Office of Pharmaceutical Quality

## NDA Reviewer Assignment Information

### 1 Approvals *[Electronic Signatures]*

<b>Content Reviewers</b>	J. Rondon, L. (OPRO/OE); D. Henry (OPRO/OE); ); S. Miller (OPQ/ONDP); O. Stephens (OPQ/ONDP); IQA Steering Committee
<b>Final Approval Signatures and Date</b>	
<b>Division Director, OPRO/OE &amp; LPD, or Designee</b>	
Title: Branch Chief, OPRO Organizational Excellence (Acting)	
Print Name: Jorge Rondon	
Signature and Date:	Signature on file
<b>Authors</b>	
Title: CMC-Lead/QAL, Branch III, DNDP-I, ONDP	
Print Name: Stephen Miller	
Signature and Date:	Signature on file
Title: Acting Branch Chief, OMPT/CDER/OPQ/ONDP/DNDPI/NDPBII	
Print Name: Olen Stephens	
Signature and Date:	Signature on file

### 2 Document History

<b>Vers ion</b>	<b>Effective Date</b>	<b>Lead Author and Working Group</b>	<b>Approving Official</b>	<b>Summary of Changes</b>
01	11/11/2015		J. Rondon	Initial